Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination with Either Bendamustine and Rituximab (BR) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects with Previously Treated Indolent Non-Hodgkin Lymphoma (iNHL)

Protocol PCI-32765FLR3001; Phase 3
AMENDMENT INT-3

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 2 and Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	10 October 2013
Amendment INT-1	10 December 2014
Amendment INT-2	10 August 2015
Amendment INT-3	29 August 2022

Amendments are listed beginning with the most recent amendment.

Amendment INT-3 (29 August 2022)

The overall reason for the amendment: To update the dose modification guidance and the data that is being collected after the clinical cutoff for the primary analysis.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule	Title update in Table 1 to define Time and Events Schedule up to clinical cutoff for the primary analysis and the time and events schedule after clinical cutoff for primary analysis. New table (Table 2) added to define the time and events schedule after clinical cutoff for primary analysis.
Time and Events Schedule 9.2.3.1 Assessment of Disease Response and Progressive Disease	The text “Efficacy Assessments” in Table 1 was update to “Disease Evaluations”
6.5.1 Study Drug (Ibrutinib or Placebo) Dose Modifications	Text was added to indicate that no dose escalation is allowed following dose reduction. Text was added to specify Grade 2 and 3 toxicities. Table 8 was added to describe ibrutinib/placebo dose modifications for cardiac failure or cardiac arrhythmias.
8.1 Concomitant Medications to be used with Caution	Revised text and added a new table (Table 9) to provide updated guidance for dose modification for ibrutinib when used concomitantly with CYP3A inhibitors. Links updated for examples of inhibitors, inducers and substrates.
9.1.5 Clinical Cutoff 9.2.1.6 Patient-Reported outcomes	Text was added to describe Table 2 and Time and Events Schedule after clinical cutoff for primary analysis, where Patient-Reported Outcomes were removed after the study primary analysis
9.4 Biomarkers and Minimal Residual Disease	Text was added to indicate that minimal residual disease will be collected until clinical cutoff for primary analysis and not after.
Throughout the protocol	Minor errors and inconsistencies were corrected, and minor clarifications were added.

Amendment INT-2 (10 August 2015)

This amendment is considered to be non-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, 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. This amendment also aligns the French and Japanese protocols with the Global protocol, and clarifies the schedule for patient-reported outcome assessments.

Applicable Section(s)	Description of Change(s)
Rationale: Clinical safety information for ibrutinib has been updated for consistency with both the ibrutinib IB and other protocols within the ibrutinib clinical development program.	
1.3.2.2. Clinical Safety of Ibrutinib; 1.3.2.2.1. Hematological Adverse Events; 1.3.2.2.2. Non-Hematological Adverse Events	Clinical safety information for ibrutinib has been updated to show currently available data for both 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, tumor lysis syndrome has been added to the non-hematological adverse event section.
Rationale: Enhanced reporting, monitoring, and review of safety events were performed during Cycle 1 for the first 10 Japanese subjects that completed Cycle 1. As this action has been completed, the additional safety monitoring in the country-specific Japanese amendment is no longer applicable, and the Japanese protocol can align with the Global protocol.	
12.4. Reporting, Monitoring, and Review of Safety Events for Japanese Subjects; Synopsis: Safety Evaluations; Attachment 5.	These sections of the country-specific amendment for Japan are no longer applicable.
Rationale: The country-specific amendment for France limits ibrutinib treatment to 3 years. As marketing authorization for ibrutinib has been received by the European Commission, and no new safety signals have been detected with longer-term use of ibrutinib as reported in the current Investigator Brochure, the country-specific amendment for France is no longer applicable. Data are not available that evaluate the safety or efficacy of discontinuing treatment in those patients who are responding to therapy. Therefore, the French protocol can align with the Global protocol where subjects are receiving continuous treatment until disease progression or unacceptable toxicity.	

Synopsis Overview of Study Design; Synopsis Dosage and Administration; Time and Events Schedule; 3.1. Overview of Study Design; Figure 1; 6.1. Study Treatment (Study Drug); 6.4. Delay of Chemotherapy; 9.1.3. Treatment Phase; 10.2. Discontinuation of Study Treatment	These sections of the country-specific amendment for France are no longer applicable.
Rationale: The schedule for patient-reported outcome assessments for has been clarified in the Time and Events Schedule.	
Time and Events Schedule	The timing of PRO assessments have been clarified to state that assessments will be taken approximately every 24 weeks, to coincide with a visit starting at Week 40, during the Post-Chemotherapy Period in the Treatment Phase and Prior to PD in the Follow-up Phase.
Rationale: A correction has been made to the criteria used to determine complete response.	
9.2.3.3. 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: To update the name of the co-development company for ibrutinib from Pharmacyclics, Inc to Pharmacyclics LLC.	
Synopsis; 1. Introduction	Pharmacyclics, Inc has been replaced by 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: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (10 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 remove requirement that only ~70% of subjects can receive 1 of the background chemotherapies as well as to implement several administrative clarifications. Updates on safety-related information (eg, monitoring for ocular symptoms and atrial fibrillation; potential risks; and guidance on co-administration with certain concomitant medications) have been implemented to align with the current Investigator's Brochure (IB).

Applicable Section(s)	Description of Change(s)
Rationale In most countries that are actively recruiting subjects, bendamustine has only recently been available. Therefore, the majority of subjects with relapsed disease who are enrolled in this study have received previous treatment with R-CHOP or similar regimens.	
3.1 Overview of Study Design; 5 Treatment Allocation and Blinding; 6.1 Study Treatment	Removed the requirement limiting the number of subjects randomized to 1 of the background chemotherapy regimens to no more than 70% of total subjects. Replaced with "The sponsor will strive towards an adequate number of subjects randomized into either of the background chemotherapy regimens."
Rationale: Instructions specific to ibrutinib/placebo administration have been updated. Restrictions for ibrutinib dosing relative to meal time has been deleted (ie, 30 minutes before eating or at least 2 hours after a meal).	
Synopsis (Dosage and Administration); 3.1 Overview of Study Design; 6.5 Study Drug Administration	Changed the time of dosing to "approximately the same time each day", independent of meal time.
Rationale: Potential risks associated with ibrutinib have been updated based on the 2014 IB (version 8.0) and new risks (cytopenia, diarrhea) have been added. Important new information is provided below (see Section 1.3.2.2 for a complete description of each risk).	
1.3.2.2 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.
Lymphocytosis and Leukostasis	There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (400,000/μL) may confer increased risk. Subjects should be closely monitored.
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 Section 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. There is no evidence of QT prolongation with increasing plasma concentrations of ibrutinib.
Diarrhea	Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea.
Infections	Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections.
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. Most rashes were mild to moderate in severity. Subjects should be closely monitored for signs and symptoms suggestive of Stevens-Johnson Syndrome.

Rationale: To provide further clarification and guidance to investigators for medications permitted during study.

8.3 Medications Permitted During Treatment	Clarified medications permitted during the study (eg, antiemetics, standard supportive care medications, prophylaxis for tumor lysis syndrome for subjects considered at risk, neutrophil growth factors, use of anti-microbial prophylaxis). Hepatitis B surface antigen positive subjects should receive appropriate prophylaxis according to local standards (eg, lamivudine).

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 serious adverse event, or any central nervous system hemorrhage/hematoma. Section 12.3.3.2 was deleted, as it is now captured within the new definition of major hemorrhage (third bullet).

Synopsis (Safety Evaluations); 9.5 Safety Evaluations (Adverse Events of Interest); 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 events 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 (Electrocardiograms)	Electrocardiograms may be repeated at any time during the study, as clinically indicated, particularly in subjects with arrhythmic symptoms (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 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.
- Statement that concomitant use of ibrutinib and anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.
- Instructions for digoxin administration relative to ibrutinib administration added.
- Clarification to instructions for anticoagulation therapy (eg, atrial fibrillation).

8.1 Precautions with Concomitant Medications	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). Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreases ibrutinib plasma concentrations 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. 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. 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: 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.	
Time and Events Schedule (footnote e); 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: On November 13, 2013 the FDA approved IMBRUVICA® (ibrutinib) for the treatment of adult patients with MCL who have received at least 1 prior therapy. Therefore, the statement regarding ibrutinib not being approved has been modified.	
Synopsis; 1. Introduction	Added statement on initial marketing approval of ibrutinib and clarified that ibrutinib has not been approved for marketing for the treatment of follicular lymphoma in any country.
Rationale: Immune modulation is a key part of follicular lymphoma response, especially with regard to the T-cell phenotypic changes. It is likely that the immune changes induced by ibrutinib, particularly the reported Th2->Th1 repolarization, may play a major role in response or resistance. This collection is being added to compare immune changes after 1 cycle of ibrutinib treatment to baseline.	
Time and Events Schedule (including footnote n)	Added additional biomarker sample on Cycle 2 Day 1.
Rationale: Administrative corrections or clarifications were made throughout the protocol.	
Throughout the protocol	References to CYP3A4/5 have been corrected to CYP3A.
Synopsis (Overview of Study Design)	Corrected incorrect treatment descriptions for each treatment arm - placebo and ibrutinib were reversed.
Synopsis (Biomarker Evaluations); 9.4 Biomarkers and Minimal Residual Disease	Deleted need for bone marrow sample for confirmation of CR for central analysis, as analysis is only done locally. Clarification of blood sampling and analysis for biomarkers and residual disease.

Time and Events Schedule	Clarification footnotes added: • Added window of ±2 days and ±4 days for the Chemotherapy and Post-Chemotherapy Periods, respectively. • Only a limited symptom-directed physical examination is required during treatment, including inquiry of ocular symptoms. • Progression needs to be confirmed by the sponsor medical monitor before subsequent therapy is started. • Clarified text on screening evaluations for Hepatitis B and C. • Clarified that during the Follow-up phase, assessments may be performed up to 16 weeks for subjects who had not progressed. • Clarified that response assessments may be repeated as clinically indicated to confirm response or progression.
Table 1	Correction made to CR/CRu rate for van Oers Blood 2006 data.
1 Introduction	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: 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.
1.2 Chemo-immunotherapy Treatment of Previously Treated iNHL	Moved sentence referring to current ibrutinib IB from Section 1.2 to a more appropriate location (ie, Section 1.3, Ibrutinib Background).
1.3.1 Clinical Pharmacokinetic Data	Correction to number of subjects exposed to mild/moderate inhibitors, per current IB.
1.3.2.2.3 Combination Therapy Studies	Updated OSU 1002 and PCI-32765DBL1002 study summaries per current publications.
4.1 Inclusion Criteria	Clarified that evidence of and clinical signs of pathological transformation cannot be present at initial histological diagnosis (Criterion 2); Other minor editorial clarifications implemented based on site and monitor feedback (Criteria 3 and 4). Revised units for consistency across the protocol for absolute neutrophil count and platelets (Criterion 7).
4.2 Exclusion Criteria; Section 9.5 Safety Evaluations	Streamlined text on exclusion of subjects with a history of HIV or active Hepatitis B and C infection (Criterion 12).
6.1 Study Treatment	Definition of BR sensitivity added.
8 Concomitant Therapy	Deleted statement causing confusion at sites: Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.
8.1 Concomitant Medication to be Used with Caution	Deleted 4th paragraph, as pharmacokinetic collections for subjects who received moderate or strong CYP inhibitors are not being performed in this study.
9.1.2 Screening Phase	Clarified wording on confirmation of FL or MZL disease at screening.
9.1.3 Treatment Phase	Clarified when PRO questionnaires should be administered.
9.1.4 (Posttreatment Phase [Follow-up]); 9.2.3.1 Assessment of Disease Response and Progressive Disease	Clarified that progression needs to be confirmed by the sponsor medical monitor before subsequent therapy is started.

9.2.1.3 Bone Marrow Assessment	Clarified that repeat bone marrow evaluation includes bone marrow aspirate and biopsy.
9.2.1.6 Patient-reported Outcomes	Corrected typographical error: EQ-5D-5L includes 5 separate questions, not questionnaires.
9.5 Echocardiogram and MUGA Scans	Clarified that an echocardiogram or MUGA scan is mandatory at screening for all subjects, not just those who are assigned to receive R-CHOP.
10.2 Discontinuation of Study Treatment	Clarified that subjects with radiographic progression without clinical progression who have not started alternate therapy may continue to receive study treatment at the discretion of the investigator.
11.3.4 Patient-Reported Outcomes	Clarified that descriptive statistics will also be performed for Fact-Lym.
11.8 Data Monitoring Committee	Increased the safety review times from 1 month to 2 months.
12.3.1 All Adverse Events	Clarified the interval of adverse event collection (ie, until 30 days after the last dose of ibrutinib or the start of subsequent systemic anticancer therapy if earlier).
References	References updated based on additions/deletions made.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination with Either Bendamustine and Rituximab (BR) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects with Previously Treated Indolent Non-Hodgkin Lymphoma (iNHL)

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is a first-in-class, potent, orally-administered covalently-binding small molecule inhibitor of Bruton's tyrosine kinase currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC for the treatment of B-cell malignancies. The initial approval of ibrutinib was received on 13 November 2013 by the United States Food and Drug Administration for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. Ibrutinib has not been approved for marketing for the treatment of follicular lymphoma (FL) in any country.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

The primary objective of this study is to evaluate whether the addition of ibrutinib to bendamustine and rituximab (BR) combination or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP**)** combination will result in prolongation of progression-free survival (PFS) compared with either BR or R-CHOP alone in subjects with previously treated iNHL (follicular lymphoma [FL] or marginal zone lymphoma [MZL]).

Secondary Objectives

The secondary objectives are to compare treatment groups in terms of overall survival, complete response rate (CR), overall response rate ORR (CR + partial response [PR]), duration of response, patient-reported lymphoma symptoms and concerns as measured by the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym), and safety of ibrutinib when combined with BR or R-CHOP.

Exploratory Objectives

The exploratory objectives are to evaluate time-to-next treatment, minimal residual disease (MRD) negative rate in FL subjects, and patient-reported outcomes (PRO) related to general health status utilizing EuroQol (EQ-5D-5L), to characterize the pharmacokinetics of ibrutinib and to explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information.

Hypothesis

The primary hypothesis of the study is that ibrutinib in combination with either BR or R-CHOP compared with either BR or R-CHOP alone will prolong PFS in subjects with previously treated iNHL (FL or MZL).

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study in approximately 400 subjects with FL or MZL. The study will include a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase.

Eligible subjects will be stratified by background chemotherapy treatment, refractory versus relapsed disease, iNHL histology, and number of prior lines of therapy. Subjects will be randomized in a 1:1 ratio to either Treatment Arm A (background chemotherapy + placebo) or Treatment Arm B (background chemotherapy + 560 mg of ibrutinib). All subjects will receive 6 cycles of background chemoimmunotherapy with either BR or R-CHOP in combination with either placebo (Arm A) or

ibrutinib (Arm B). Selection of background therapy will be based on prior treatment history and cardiac function. After completion of background therapy, study drug (ibrutinib or placebo) will continue until disease progression, unacceptable toxicity, or study end.

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 further conduct of the study.

SUBJECT POPULATION

Key eligibility criteria include: 18 years of age or older; histologically confirmed (by central laboratory) diagnosis of B-cell iNHL, with histological subtype limited to the following (a) FL Grade 1, 2, or 3a or (b) MZL (splenic, nodal, or extra-nodal); disease which has relapsed or was refractory (failure to achieve PR or CR after the most recent treatment) after prior chemoimmunotherapy; at least 1 prior treatment with a CD20 antibody combination chemotherapy regimen; at least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma; Eastern Cooperative Oncology Group performance status grade 0 or 1.

DOSAGE AND ADMINISTRATION

Study drug (ibrutinib 560 mg or placebo) will be administered orally at approximately the same time each day along with background chemotherapy. Background BR (28-day cycles) consists of bendamustine hydrochloride 90 mg/m^2 intravenously (IV) on Days 1 and 2 of Cycles 1 to 6 and rituximab 375 mg/m^2 IV on Day 1 of Cycles 1 to 6. Background R-CHOP (21-day cycles) consists of rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, and vincristine 1.4 mg/m^2 IV [maximum total 2 mg] on Day 1 of Cycles 1 to 6 along with prednisone 100 mg orally on Days 1 to 5 of Cycles 1 to 6. Study drug will continue to be administered beyond Cycle 6 until disease progression, unacceptable toxicity, or study end.

EFFICACY EVALUATIONS/ENDPOINTS

Assessment of tumor response and progression will be conducted in accordance with the Revised Response Criteria for Malignant Lymphoma. Efficacy evaluations may include computed tomography scans, magnetic resonance imaging, positron emission tomography using [18F]-fluorodeoxyglucose, bone marrow aspirate and biopsy, physical examination including lymphoma B symptoms, or other procedures as necessary. Subject lymphoma related symptoms and concerns will be measured by the lymphoma subscale of the FACT-Lym and health status will be measured by the EQ-5D-5L.

The primary endpoint is PFS as assessed by the treating physician. Subjects who discontinue treatment prior to disease progression will have regularly scheduled disease evaluations until disease progression, death, or study end, whichever occurs first. For all subjects, survival and subsequent antineoplastic therapy data will be collected until death, lost to follow-up, withdrawal of consent, or study end.

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. Pharmacokinetic parameters (eg, oral clearance) and/or metrics of systemic exposure (eg, area under the plasma concentration-time curve [AUC], maximal plasma concentration [C_{max}]) will be evaluated. Parameters describing the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information will also be evaluated.

BIOMARKER EVALUATIONS

For subjects with FL who have achieved CR, blood samples will be collected at scheduled disease assessment visits for assessment of MRD, until clinical cutoff for the primary analysis. A portion of the formalin-fixed, paraffin-embedded tissue block or slides obtained at baseline may be used for central assessment of MRD.

SAFETY EVALUATIONS

Safety evaluations include: adverse event monitoring, physical examinations, evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, coagulation, serum chemistry, serum immunoglobulin [IgG, IgM, IgA], and beta$_2$-microglobulin). Adverse events that occur between the signing of the informed consent through 30 days after subjects have completed study treatment will be collected. 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 an adverse event of special interest and will require enhanced reporting and data collection.

STATISTICAL METHODS

The study will enroll approximately 400 subjects (about 200 subjects to each arm), based on the following considerations:

- 1:1 randomization ratio between the 2 treatment arms;
- Target hazard ratio of 0.7. Assuming the median PFS for the control arm (BR or R-CHOP + placebo) is 20 months from randomization, a target hazard ratio of 0.7 corresponds to an 8.6-month increase in median PFS for the treatment arm (BR or R-CHOP +ibrutinib) relative to the control (ie, 20.0 months versus 28.6 months, respectively);
- Minimum 80% power;
- 2-sided overall significance level of 0.05;
- One interim analysis for efficacy at 60% of the planned total PFS events.

Three clinical cutoffs are planned. The first 2 clinical cutoffs will occur when approximately 151 and 252 PFS events have been observed, respectively. The interim analysis and the primary analysis (ie, final analysis of the primary endpoint PFS) will take place at these 2 clinical cutoffs, respectively. The last cutoff will occur at the time of the end of study, when approximately 50% of the randomized subjects have died, or the sponsor terminates the study, whichever comes first.

The primary efficacy analysis will be based on PFS and will be performed using the ITT population, which is defined as all randomized subjects. The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The stratified log-rank test will be used to compare survival curves of PFS between the 2 treatment groups. Hypothesis testing for the interaction between background therapy and treatment will be performed.

Adverse events will be summarized and listed. Summary statistics and graphical displays may be presented for clinical laboratory parameters. Descriptive statistics of changes from baseline for vital signs and physical examination will be summarized.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule until the study Primary Analysis

	Screening Phase (within 30 days of randomization)	Treatment Phase			Follow up Phase		
		Chemotherapy Period Cycle 1 to Cycle 6 [c]		*Post-Chemotherapy Period* [f]	EOT (within 30 days of last dose)	Prior to PD: every 12 weeks, After 3 years: every 24 weeks	After PD: every 24 weeks
		Day 1	Day 2	Every 8 weeks Starting at Cycle 7			
Screening/Administrative							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical and disease history	X						
iNHL (FL or MZL) diagnosis [a]	X						
Urine or serum pregnancy test [b]	X						
Drug Administration (within 72 hours of randomization)							
BR							
Rituximab 375 mg/m²		X					
Bendamustine hydrochloride 90 mg/m²		X	X				
R-CHOP							
Rituximab 375 mg/m²		X					
Cyclophosphamide 750 mg/m²		X					
Doxorubicin 50 mg/m²		X					
Vincristine 1.4 mg/m²		X					
Prednisone 100 mg		Day 1-5					
Study drug: **Arm A**: Placebo (4 capsules) **Arm B**: Ibrutinib 560 mg (4 capsules)		<----------Continuous---------->					
Dispense study drug, check drug accountability		X		X			
Safety Assessments							
Height	X						
Vital signs and ECOG PS	X	X		X			
Body surface area; weight		X					
Electrocardiogram [d]	X						
Echocardiogram or MUGA (if receiving R-CHOP must be within normal limits) [d]	X						
Disease-related symptoms, physical exam	X	X[e]		X[e]	X	X	

Table 1: Time and Events Schedule until the study Primary Analysis

	Screening Phase (within 30 days of randomization)	Treatment Phase			Follow up Phase		
		Chemotherapy Period Cycle 1 to Cycle 6 [c]		*Post-Chemotherapy Period* [f]	EOT (within 30 days of last dose)	Prior to PD: every 12 weeks, After 3 years: every 24 weeks	After PD: every 24 weeks
		Day 1	Day 2	Every 8 weeks Starting at Cycle 7			
Disease Evaluations							
PRO (FACT-Lym, EQ-5D-5L) [g]		C1, C6		Approximately every 24 weeks, to coincide with a visit, starting at Wk40	X	Approximately every 24 weeks, to coincide with a visit, starting at Wk40	once [g]
CT/MRI	X [h]	Wk12, Wk24, then every 16 weeks; after 3 years every 24 weeks (±7-day window for all visits), until PD					
PET	X [h]	At maximal tumor reduction [i]					
Bone marrow aspirate and biopsy	X [h]	At CR if positive at baseline					
Blood sample for minimal residual disease evaluations, subjects with FL		C1	For FL subjects with CR, at every disease assessment visit starting with CR visit (Wk12, Wk24, then every 16 weeks; after 3 years every 24 weeks, until PD)				
Survival status and subsequent antineoplastic therapies [j]						X	X
Clinical Laboratory Assessments							
Complete blood count	X	X [k]		X	X	X	
Serum chemistry	X	X [k]		X			
Hepatitis serologies [l]	within 60 days of randomization						
aPTT, INR, PT	X						
Serum Ig and beta 2-microglobulin	X	Wk 12, Wk 24 and Wk 40 with CT/MRI assessment			X		
Pharmacokinetics and Biomarkers							
PK sample (study drug) [m]		X					
Biomarker blood sample [n]		C1, C2			X [n]		
Ongoing Subject Review							
Concomitant medication	<--Continuous from informed consent until 30 days after last dose of study drug->						
Adverse events	<-Continuous from informed consent until 30 days after last dose of study drug->						

aPTT=activated partial thromboplastin time; BR=bendamustine and rituximab; C=cycle; CR=complete response; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=end-of-treatment; EQ-5D-5L=EuroQol; FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma; FL=follicular lymphoma; iNHL=indolent non-Hodgkin lymphoma; Ig=immunoglobulin; INR=international normalized ratio; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; MZL=marginal zone lymphoma; PCR=polymerase chain reaction; PD=disease progression; PET=positron emission tomography; PK=pharmacokinetic; PRO=patient-reported outcomes; PT=prothrombin time; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; Wk=week

a. Slides or tumor block for confirmation of diagnosis may be either newly obtained or from previous biopsy; any remaining sample may be used for MRD and biomarker evaluations for FL subjects only.
b. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during the subject's participation in the study.
c. Window of ±2 days.
d. May be repeated during the study when clinically warranted.
e. 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).
f. Window of ±4 days.
g. EQ-5D-5L and lymphoma subscale of the FACT-Lym should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician. Following disease progression, collect once approximately 24 weeks after PD, preferably in person but acceptable via telephone contact with subject.
h. At screening within 60 days of randomization; may be repeated as clinically indicated to confirm response or progression.
i. Maximal tumor reduction defined as time of CR or when 2 consecutive CT scans show no further tumor reduction.
j. Progression needs to be confirmed by the sponsor medical monitor before subsequent therapy is started.
k. 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 drug.
l. 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 negative for Hepatitis surface antigen but positive for Hepatitis B core antibody do not require PCR testing and may be included in the study with prophylaxis. All other subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization, and may be included in the study following consultation with an infectious disease specialist. 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.
m. Predose sample to be obtained on Day 1 in Cycles 1, 2 and 3, and postdose on Day 1 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.
n. Day 1 of Cycle 1, Day 1 of Cycle 2, and at the time of suspected disease progression; or at EOT for subjects without disease progression.
o. May be performed up to 16 weeks.

Table 2: Time and Events Schedule After the study Primary Analysis

	Treatment Phase		Posttreatment Follow-up Phase	
	Every 8 weeks (±4 days)	**End of Treatment Visit (Within 30 days after last dose)**	**Prior to Disease Progression (Every 24 weeks ±4 weeks)**	**Following Disease Progression (Every 24 weeks ±4 weeks)**
Administer ibrutinib	<----------Continuous---------->			
Dispense ibrutinib	X			
Check drug accountability	X	X		
SAEs; Grade ≥3 AEs; AEs resulting in dose interruption, reduction, or discontinuation; major hemorrhages[a]	<---- Continuous from informed consent to 30 days after the last dose of study treatment or until the start of a subsequent systemic anti-lymphoma therapy, if earlier ---->			
Prohibited concomitant medications and concomitant medications related to SAEs	<---- Continuous from informed consent to 30 days after the last dose of study treatment or until the start of a subsequent systemic anti-lymphoma therapy, if earlier ---->			
New malignancies[b]	<---------- Continuous ---------->			
Laboratory assessments	Per standard of care. Record in eCRF if indicative of the onset and recovery from an adverse event			
Vital signs (heart rate and blood pressure)	Assess at each visit. Record in eCRF if indicative of the onset and recovery from an adverse event			
Physical examination	X	X	Per standard of care	
Disease evaluations	<----------Per standard of care---------->			
Survival status			X[c]	X
Subsequent anti-lymphoma therapies[d]		X		X

[a] Lower grade AEs may be reported by the investigator if considered relevant or important.
[b] New malignancies of any grade should be reported throughout the study on the New Malignancies eCRF and (if treatment-emergent) on the Adverse Event eCRF.
[c] Contact the subject as needed to assess survival status so that a disease evaluation or survival contact occurs at least every 24 (±4) weeks.
[d] Best response as well as progressive disease on subsequent anti-lymphoma therapy will be collected.

Key: AE = adverse event; eCRF = electronic case report form; SAE = serious adverse event.

ABBREVIATIONS

ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours post dose
AUC_{last}	area under the concentration-time curve to the last quantifiable concentration
BCL2	B-cell lymphoma 2
BCR	B-cell antigen receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CYP	cytochrome P450
CR(s)	complete response(s)
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
eDC	electronic data capture
EOT	end-of-treatment
EQ-5D-5L	EuroQol; European Quality of Life Questionnaire
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCR	fludarabine, cyclophosphamide, rituximab
FFPE	formalin fixed, paraffin-embedded
FL	follicular lymphoma
GCP	Good Clinical Practice
GTD	greatest transverse diameter
HBV	hepatitis B virus
β-hCG	beta human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
iNHL	indolent non-Hodgkin lymphoma
INR/PT	international normalized ratio/prothrombin time
ITT	intent-to-treat
IRB	Independent Review Board
IWRS	interactive web response system
IV	intravenous(ly)
IVRS	interactive voice response system
MCL	mantle cell lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multiple uptake gated acquisition
MZL	marginal zone lymphoma

NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PP	per protocol
PQC	product quality complaint
PR(s)	partial response(s)
aPTT	activated partial thromboplastin time
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CVP	rituximab, cyclophosphamide, vincristine, and prednisone
REAL	Revised European-American Lymphoma
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
TTNT	time-to-next treatment
TTW	time to worsening
ULN	upper limit of normal
WBC	white blood cell
WM	Waldenström's macroglobulinemia

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 and Pharmacyclics LLC for the treatment of B-cell malignancies. 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. The initial approval of ibrutinib was received on 13 November 2013 from the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. Ibrutinib has not been approved for marketing for the treatment of follicular lymphoma (FL) in any country. Ibrutinib and PCI-32765 and "ibrutinib" refer to the same molecule; hereafter, "ibrutinib" will be used.

1.1. Indolent Non-Hodgkin Lymphoma

Indolent non-Hodgkin lymphoma (iNHL) was initially defined within the Revised European American Lymphoma (REAL) classification and comprises FL, small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (WM). These lymphomas are generally highly responsive to a variety of therapies, but are considered incurable with conventional therapies. The majority of patients with indolent lymphomas will relapse and suffer substantial morbidity as well as mortality related to the persistence or recurrence of their disease. Together, FL and MZL account for the vast majority of all indolent lymphomas.

Follicular lymphoma is the one of the most common types of non-Hodgkin lymphoma (NHL) accounting for approximately 22% of cases (NHL Classification Project 1997) and for about 70% of indolent lymphomas (NHL Cyber family web site). Most cases have a t(14;18) translocation, which juxtaposes B-cell lymphoma 2 (BCL2) with the IgH locus and results in the deregulated expression of BCL2 (NCCN 2013). Marginal zone lymphomas are a group of B-cell malignancies originating from B lymphocytes that are normally present in the marginal zone of the lymphoid follicles of the spleen, lymph nodes, and lymphoid tissue (Kahl 2008). Marginal zone lymphomas account for approximately 10% of all NHLs (NHL Classification Project 1997).

1.2. Chemo-immunotherapy Treatment of Previously Treated iNHL

For patients with relapsed iNHL, there are several choices of therapy. Treatment choices depend on stage of disease, symptoms, patient age, overall ability to withstand the associated side effects of the regimen, and comorbidities. Treatment guidelines provided by both the National Comprehensive Cancer Network (NCCN 2013) and the European Society for Medical Oncology (Dreyling 2011) provide similar evidence-based recommendations.

When treatment is given, initial therapy may include rituximab (Rituxan®) as a single agent or in combination with 1 or more cytotoxic drugs. Response rates in excess of 85% are observed with

many different combinations (Peterson 2003; Hiddemann 2005; Marcus 2007; Czuczman 2005; Rummel 2012). In addition, when rituximab is used as maintenance treatment, the response rate and disease-free interval increase (Colombat 2001; Hainsworth 2003; Salles 2010).

For patients with relapsed iNHL, 2 of the most common/most representative treatment regimens in the relapsed setting are bendamustine and rituximab (BR) and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The use of chemoimmunotherapy regimens such as R-CHOP and BR regimens in the relapsed setting is primarily informed by published frontline data. A summary of results from studies in patients with iNHL treated with either BR or R-CHOP is provided in Table 3.

Table 3: Descriptive Summary of Responses to Agents Evaluated for the Treatment of Indolent non-Hodgkin Lymphoma

	Rummel et al JCO 2005	Robinson et al JCO 2008	Fowler et al JCO 2011	Friedberg et al Blood 2011	Van Oers et al Blood 2006
N	63	67	63	30	234
Population	Relapsed low-grade lymphoma	Relapsed low-grade lymphoma	R/R FL	R/R iNHL and MCL (n=7)	R/R FL
Rituximab Exposed	0%	40%	100%	100%	0%
Regimen	BR	BR	BR + bortezomib	BR + bortezomib	R-CHOP
CR/CRu	60%	55%	53%	52%	30%
Median PFS (months)	24	23	15	19	33

BR=bendamustine and rituximab; CR=complete response; CRu=complete response unconfirmed; FL=follicular lymphoma; iNHL=indolent non-Hodgkin lymphoma; MCL=mantle cell lymphoma; PFS=progression-free survival; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R=relapsed/refractory.

In a Phase 2 clinical study of 63 subjects with iNHL and MCL in the relapsed and refractory setting, the combination of BR has been shown to be efficacious with an overall response rate (ORR) of 90%, complete response (CR) rate of 60%, and median progression-free survival (PFS) of 24 months (Rummel 2005). These data were confirmed in a follow up study of 67 patients with relapsed indolent NHL or MCL (Robinson 2008), with a PFS of 23 months. Notably, all patients in the Rummel study and most in the Robinson study were rituximab naïve. More relevant to current clinical practice are the results from 2 clinical studies evaluating BR+Velcade® (bortezomib) in treating rituximab exposed and relapsed iNHL patients (Fowler 2011; Friedberg 2011). In these studies, the median PFS ranged from 15 to 19 months, in contrast to the longer median PFS observed in rituximab-naïve populations. In the VERTICAL study, 63 subjects with relapsed FL were treated with bendamustine at 90 mg/m^2 in combination with rituximab and bortezomib with an ORR of 88% (53% CR) and median PFS of 14.9 months (Fowler 2011). A similar regimen was studied in 30 subjects with relapsed iNHL (n=23) and MCL (n=7) with an ORR of 83% (52% CR) (Friedberg 2011). The 2-year PFS for the response evaluable population was 47%.

The role of R-CHOP treatment in patients with relapsed/refractory FL has been evaluated (van Oers 2006). About 80% of patients had received only 1 prior treatment, almost equally consisting of single-agent therapy (mainly chlorambucil) or polychemotherapy. No patients had received prior rituximab. Patients were randomized to remission induction with 6 cycles of standard CHOP (n=231) or R-CHOP (n=234). With a median follow-up of 39.4 months, median PFS was 33.1 months for the R-CHOP group versus 20.2 months for the CHOP group ($p<0.001$). This study also demonstrated improved PFS among patients who received rituximab maintenance therapy after achieving CR or partial response (PR) (van Oers 2010). Maintenance rituximab is often incorporated into front-line regimens. The added benefit, however, appears to be limited to rituximab naïve patients and is not standard in the relapsed setting (NCCN 2013).

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.

1.3. Ibrutinib Background

For the most current comprehensive nonclinical and clinical information regarding ibrutinib, including information on adverse drug reactions, refer to the latest version of the ibrutinib Investigator's Brochure and supplements/addenda.

Nonclinical Studies

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site (Pan 2007). The covalent bond formed between ibrutinib and Cys-481 is highly stable, resulting in sustained inhibition of the target. Ibrutinib, based on available clinical exposure data, is extensively metabolized. The contribution of metabolites to the overall activity is unknown. The mechanism of action of ibrutinib can be summarized as follows:

BTK Target Inhibition

- Ibrutinib forms a stable covalent bond specifically with Cys-481 in the BTK active site.
- Ibrutinib is a highly potent BTK inhibitor with half-maximal inhibitory concentration (IC_{50}) of 0.39 nM.
- Oral administration of ibrutinib at 420 to 560 mg once daily results in sustained target inhibition, while circulating drug is rapidly cleared.

Antitumor Activity

- Ibrutinib inhibits B-cell receptor (BCR) and chemokine-receptor signaling pathways in malignant B cells.
- Ibrutinib disrupts integrin-dependent B-cell migration and adhesion in vitro.
- Ibrutinib promotes egress of malignant B cells from tissues and prevents homing of these cells to tissues.

Thus, ibrutinib, via a mechanism of BTK inhibition, overcomes the BCR- and chemokine-controlled retention of malignant B cells in their supportive microenvironments, and thereby is able to disrupt the pathogenesis of several B-cell malignancies.

1.3.1. Clinical Pharmacokinetic Data

In vitro preclinical data show that ibrutinib is metabolized primarily by cytochrome P450 (CYP) 3A4/5. Its bioavailability is variable and relatively low (data on file). In healthy fasted subjects, significant pharmacokinetic interactions were observed in drug-drug interaction (DDI) studies with ketoconazole (PCI-32765CLL1002) and rifampin (PCI-32765CLL1010), a strong CYP3A inhibitor and inducer, respectively. In a study with 18 healthy male subjects dosed with 120 mg ibrutinib alone followed by 40 mg ibrutinib in combination with 400 mg once daily oral ketoconazole, dose-normalized area under the plasma concentration-time curve (AUC) to the last quantifiable concentration (AUC_{last}) and maximum plasma concentration (C_{max}) of ibrutinib increased by 24-fold and 29-fold, respectively. In another study with healthy males and females dosed with 560 mg ibrutinib alone (n=18) followed by ibrutinib in combination with 600 mg once daily oral rifampin (n=17), AUC_{last} and C_{max} of ibrutinib decreased by 10-fold and 13-fold, respectively.

There is no intra-patient DDI data comparing ibrutinib exposure with and without concomitant CYP3A inhibitors. However, exposure data from 37 subjects taking concomitant mild and/or moderate inhibitors did not reveal major differences in absolute exposures. Approximately 90% of the subjects treated with mild and/or moderate CYP3A inhibitors had ibrutinib exposure within the range of those (n=76) who did not receive the inhibitors. For those subjects with exposure above this range, the ibrutinib AUC was still ≤2-fold the upper limit of the range observed in absence of inhibitors. No exposure data for concomitant administration of ibrutinib with strong inhibitors (treatment with strong inhibitors on study was after the pharmacokinetic sampling period) of CYP3A is available in these subjects. Clinical safety data in subjects treated with mild, moderate, or strong CYP3A inhibitors did not reveal a meaningful increase in adverse events.

Guidance on concomitant use of ibrutinib/placebo with CYP3A inhibitors or inducers is provided in Section 8.1.

In a food effect study in 43 healthy subjects (PCI-32765CLL1001), administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to administration either 30 minutes before or 2 hours after a meal (the recommended dosing conditions). When ibrutinib was taken 30 minutes after a high fat breakfast (fed condition), the exposure (AUC_{last}) was comparable to the recommended dosing conditions of either 30 minutes before or 2 hours after a meal.

1.3.2. Clinical Studies of Ibrutinib

1.3.2.1. Clinical Efficacy of Ibrutinib

Efficacy results from Study PCYC-04753 suggest that ibrutinib has activity as a single-agent in the treatment of subjects with relapsed or refractory iNHL. Currently a large, multicenter study (PCI-32765FLR2002) of ibrutinib in chemoimmunotherapy resistant FL is ongoing.

Study PCYC-04753

Study PCYC-04753 was a multicenter, open-label, dose-escalation, Phase 1 study of ibrutinib in recurrent B-cell malignancies (relapsed or refractory NHL, chronic lymphocytic leukemia (CLL), and WM with a minimum of 6 subjects per cohort). Five dose levels (1.25, 2.5, 5.0, 8.3, and 12.5 mg/kg/day) were administered. In these dosing cohorts, each treatment cycle consisted of 28 consecutive days of once daily dosing followed by a 7-day rest period. Two additional dose groups at 8.3 mg/kg/day and 560 mg/day (fixed dose) were also evaluated using a 35-day cycle with no rest period ("continuous dosing" and “fixed” cohorts, respectively).

Sixteen subjects with a diagnosis of FL were enrolled and treated in Study PCYC-04753 (PCYC 04753 CSR). Median age was 60 years (range, 41 to 71 years). Equal numbers of male and female subjects were enrolled (n=8). Median time since initial diagnosis was 54 months (range, 19 to 186 months). Subjects had received a median of 3 prior therapies (range, 1 to 6 therapies). Approximately one third (31%) had received prior radiotherapy.

Of the 11 subjects with FL included in the efficacy evaluable population, 3 subjects (27%) had a best response of CR, and 2 subjects (18%) had a best response of PR, for an ORR of 45%. Five subjects (45%) had stable disease and 1 subject (9%) had progressive disease. Median time on ibrutinib was 6.7 months (range, 0.2 to 17.1 months). Median PFS was 13.4 months. Median follow-up time was 8.8 months (range, 3.3 to 17.3 months). Three subjects with MZL were also enrolled, with 1 PR noted. The median PFS for all 3 subjects was 7 months (95% confidence interval [CI]: 2-9 months).

1.3.2.2. Clinical Safety of Ibrutinib

As of 6 April 2015, 1071 subjects have been treated with ibrutinib monotherapy and 423 subjects have been treated with ibrutinib combination therapy in sponsor-initiated clinical studies in B-cell lymphomas. Because ibrutinib is in clinical development, its 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.

1.3.2.2.1. Hematological Adverse Events

Cytopenias

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

Lymphocytosis and Leukostasis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL treated with ibrutinib. This effect has also been observed in some subjects 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 few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/ μL) has been observed in some subjects. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

1.3.2.2.2. Non-hematological Adverse Events

Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria (see also Section 12.3.3.1). Subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists.

Subjects in the current study will be monitored closely for hemorrhagic adverse events (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 8.1.

Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinically for atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically and if indicated, have an electrocardiogram (ECG) performed. For atrial fibrillation that persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.

There is no evidence of QT prolongation with increasing plasma concentrations of ibrutinib. Guidance on the use of medications known to cause QT prolongation is provided in Section 8.1.

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 described in Section 6.5.1.

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. Although causality has not been established, cases of progressive multifocal leukoencephalopathy have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

Second Primary 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 PCYC-1112-CA. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS) was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and medications for gout (allopurinol) known to be associated with SJS. Subjects should be closely monitored for signs and symptoms suggestive of 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.

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.

1.3.2.2.3. Combination Therapy Studies

The safety of ibrutinib administered with rituximab-containing therapy has also been evaluated in 2 clinical studies, (Study PCYC1108-CA and Study PCI-32765DBL1002), and in an investigator-initiated study (Study OSU10052). These data suggest that ibrutinib can be combined with these regimens at their usual doses.

Study PCYC 1108-CA

In Study PCYC-1108-CA, ibrutinib (420 mg/day) is administered to subjects with CLL/SLL in combination with either the FCR regimen (fludarabine, cyclophosphamide, and rituximab) or the BR regimen. Bendamustine plus rituximab is administered intravenously (IV) for a maximum of 6 cycles. One cycle is 28 days. Subjects receive bendamustine 70 mg/m² on Day 1 and 2 of each cycle. For Cycle 1 only, rituximab is given at a dose of 375 mg/m^2 on Day 1; alternatively, the rituximab dose could be divided between Day 1 and Day 2 per institution standards for subjects considered at risk for infusion reactions. Rituximab is given at a dose of 500 mg/m² on Day 1 of subsequent cycles of therapy.

Thirty subjects received ibrutinib in combination with BR. All subjects reported 1 or more treatment-emergent adverse events. The most common adverse events have been diarrhea (21 subjects; 70.0%), nausea (20 subjects; 66.7%), and fatigue (14 subjects; 46.7%). Neutropenia was the most common hematologic toxicity (12 subjects; 40.0%), followed by thrombocytopenia (5 subjects; 16.7%), and anemia and febrile neutropenia (2 subjects each; 6.7%). Many of the adverse events occurring in greater than 10% of subjects reflect the adjunctive chemotherapy.

Overall, 66.7% of subjects have experienced at least one Grade 3 or 4 event during treatment. The most common were neutropenia (12 subjects; 40%), fatigue and maculopapular rash (3 subjects each; 10.0%), and thrombocytopenia, febrile neutropenia, and cellulitis (2 subjects each; 6.7%).

Overall, 20% of treated subjects have experienced at least 1 serious adverse event. Febrile neutropenia and cellulitis were the most common serious events reported in 2 (6.7%) subjects each. The system organ classes most frequently affected with a serious adverse event have been Blood and Lymphatic system (6.7%) and Infections (6.7%). No serious adverse events in the Hepatic, Renal, or Cardiac system organ classes have been reported. Four (13.3%) subjects experienced a serious adverse event deemed related to ibrutinib— including febrile neutropenia reported in 2 (6.7%) subjects, and cellulitis and tumor lysis syndrome, reported in 1 (3.3%) subject each. In general, the serious adverse events reported to date have been commensurate with the disease state of this population.

There were no treatment-emergent adverse events resulting in premature discontinuation of ibrutinib therapy. Events leading to discontinuation of bendamustine and/or rituximab were reported in 20% of subjects, of which neutropenia was the most commonly reported in this category (3 subjects, 10.0%). No subjects died during the study and within 30 days of last study treatment.

This study demonstrated that ibrutinib can be safely combined with BR. The toxicity profile of combination ibrutinib and BR is similar to that of BR alone (O'Brien 2012).

Study OSU 10052 (Investigator-initiated Study of BR in Combination with Ibrutinib)

This study (Study OSU 10052) was an investigator-initiated Phase 1 study of ibrutinib in combination with BR in subjects with relapsed/refractory NHL. Treatment consisted of rituximab at a dose of 375 mg/m^2 on Day 1, bendamustine 90 mg/m^2 on Days 1 and 2, and escalating doses

of ibrutinib (280 or 560 mg) on Days 1 to 28 every 28 days for 6 cycles, followed by ibrutinib alone until progression. Forty-eight subjects (37 males) with a median age of 62 (range 23 to 84 years) previously treated with a median of 3 prior therapies (range 1 to 10 prior therapies) were enrolled. Histologies included MCL (n=17), diffuse large B-cell lymphoma (DLBCL, n=16), transformed NHL (n=2), FL (n=12), and MZL (n=1) (Maddocks 2014).

No dose-limiting toxicities (DLTs) have been observed. Subjects received a median of 8 cycles, with 26 subjects completing 6 cycles and continuing ibrutinib alone in Cycles 7 to 34. Grade 3 and 4 toxicities included lymphopenia (77%), neutropenia (33%), rash (25%), and thrombocytopenia (19%). The recommended Phase 2 dose of ibrutinib in combination with R-bendamustine in subjects with NHL is 560 mg.

Study PCI-32765DBL1002

Study PCI-32765DBL1002 was an open-label, nonrandomized, multicenter, dose-escalation study to establish the recommended Phase 2 dose of ibrutinib combined with standard R-CHOP therapy in subjects with newly diagnosed CD20-positive B-cell NHL, including DLBCL, FL, and MCL. Subjects were assigned to cohorts of increasing oral daily doses of ibrutinib (280, 420, and 560 mg) administered in combination with R-CHOP. Of the 33 subjects treated with the ibrutinib+R-CHOP combination in Study PCI32765DBL1002; 21 subjects received the recommended Phase 2 dose of 560 mg/day.

In the all treated population (N=33), all subjects had at least 1 adverse event and 27 (82%) had Grade 3 or higher adverse events (Younes 2014). The most common Grade 3 or higher adverse events included neutropenia (73%, 24 subjects), thrombocytopenia (21%, 7 subjects), and febrile neutropenia and anemia (18% each, 6 subjects). The most frequently reported serious adverse events were febrile neutropenia (18%, 6 subjects) and hypotension (6%, 2 subjects).

Thirteen (39%) of 33 subjects had an adverse event leading to dose modification of any of the study drugs; 3 (9%) subjects had serious adverse events leading to dose reduction (Grade 3 febrile neutropenia and pyrexia, Grade 3 febrile neutropenia, and Grade 3 diarrhea, in 1 subject each). Eleven (34%) of 32 subjects had single-dose reductions of vincristine and 1 subject (3%) each had 1 or 2 dose reductions of cyclophosphamide, doxorubicin, or prednisone; no rituximab dose reductions were noted. Five (16%) subjects had an ibrutinib dose reduction. Nine (27%) subjects had an adverse event leading to treatment discontinuation of 1 or more study drug. One subject died during the study, but cause of death (suicide) was considered unrelated to treatment.

1.4. Overall Rationale for the Study

With conventional chemotherapy, even if combined with radiotherapy, advanced-stage iNHL is incurable (Relander 2010). Responsiveness to therapy and duration of response both decline with repeated treatments, with death generally resulting from the disease (Montoto 2007). For patients with significant tumor burden or progressive disease, chemoimmunotherapeutic options are preferred (NCCN 2013). Chemoimmunotherapy regimens such as R-CHOP and BR are the most commonly used regimens in the relapsed setting, primarily informed by published frontline data.

Outcomes of chemoimmunotherapy in the relapsed setting are poor, regardless of the background chemotherapy selected, particularly for patients with prior exposure to rituximab-containing chemoimmunotherapy. While there are a number of available therapies for patients with previously treated iNHL, these agents provide limited clinical benefit to these patients, and none of these treatments are curative, highlighting the need for novel, well-tolerated, effective treatment options. Hence, there is a medical need for new treatments that can be combined with existing therapies to provide durable clinical benefit without added toxicities.

Ibrutinib, a first-in-class, potent, BTK inhibitor, has demonstrated promising activity in patients with iNHL in Phase 1 studies and in an ongoing Phase 2 study in 110 subjects with chemoimmunotherapy-resistant FL (Study PCI-32765FLR2002). Phase 1 combination studies PCYC-1108, OSU 10052, and PCI-32765DBL1002 have demonstrated that ibrutinib can be safely combined with chemoimmunotherapy regimens such as BR and R-CHOP. These data suggest that targeting BTK is a novel, safe, and potentially effective therapeutic approach in iNHL.

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 (BR) combination or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP**)** combination will result in prolongation of PFS compared with either BR or R-CHOP alone in subjects with previously treated iNHL (FL or MZL).

Secondary Objectives

The secondary objectives are to compare treatment groups in terms of the following:

- overall survival (OS)
- complete response rate (CR)
- overall response rate (ORR [CR+PR])
- duration of response (DOR)
- patient-reported lymphoma symptoms and concerns as measured by the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
- safety of ibrutinib when combined with BR or R-CHOP

Exploratory Objectives

The exploratory objectives are to evaluate:

- time-to-next treatment (TTNT)
- minimal residual disease (MRD) negative rate in FL subjects
- patient-reported outcomes (PROs), related to general health status, utilizing EuroQol (EQ-5D-5L)

- pharmacokinetics of ibrutinib and explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information

2.2. Hypothesis

The primary hypothesis of this study is that ibrutinib in combination with either BR or R-CHOP compared with either BR or R-CHOP alone will prolong PFS in subjects with previously treated iNHL (FL or MZL).

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 or R-CHOP to BR alone or R-CHOP alone in subjects with previously treated iNHL (FL or MZL).

The study will include a Screening Phase, Treatment Phase, and Posttreatment Follow-up Phase. Subject eligibility will be determined up to 30 days prior to randomization. The Treatment Phase will extend from randomization until study drug discontinuation.

All subjects will receive background therapy with either BR or R-CHOP. Selection of background therapy will be based on prior treatment history and cardiac function. The sponsor will strive towards an adequate number of subjects randomized into either of the background chemotherapy regimens.

Approximately 400 eligible subjects will be stratified by (1) background chemotherapy treatment, (2) refractory versus relapsed disease, (3) iNHL histology, and (4) number of prior lines of therapy (for definitions see Section 11.3.1). Subjects will be randomized in a 1:1 ratio to either Treatment Arm A (background chemotherapy + placebo) or Treatment Arm B (background chemotherapy + 560 mg of ibrutinib). Study drug will be administered orally at approximately the same time each day and on a continuous schedule until disease progression, unacceptable toxicity, or study end, whichever comes first.

The Posttreatment Follow-up Phase will begin once a subject discontinues study drug (ibrutinib or placebo). Subjects who discontinue for reasons other than disease progression must continue disease evaluations according to the Time and Events Schedule. The Posttreatment Follow-up Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first.

Three clinical cutoffs are planned. The first 2 clinical cutoffs will occur when approximately 151 and 252 PFS events have been observed, respectively. The interim analysis and the final analysis of the primary endpoint PFS will take place at these 2 clinical cutoffs, respectively. The last cutoff will occur at the time of the end of study, when approximately 50% of the randomized subjects have died, or the sponsor terminates the study, whichever comes first. Investigators will be informed when the cutoffs are to 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 are able to continue treatment after the end of the study.

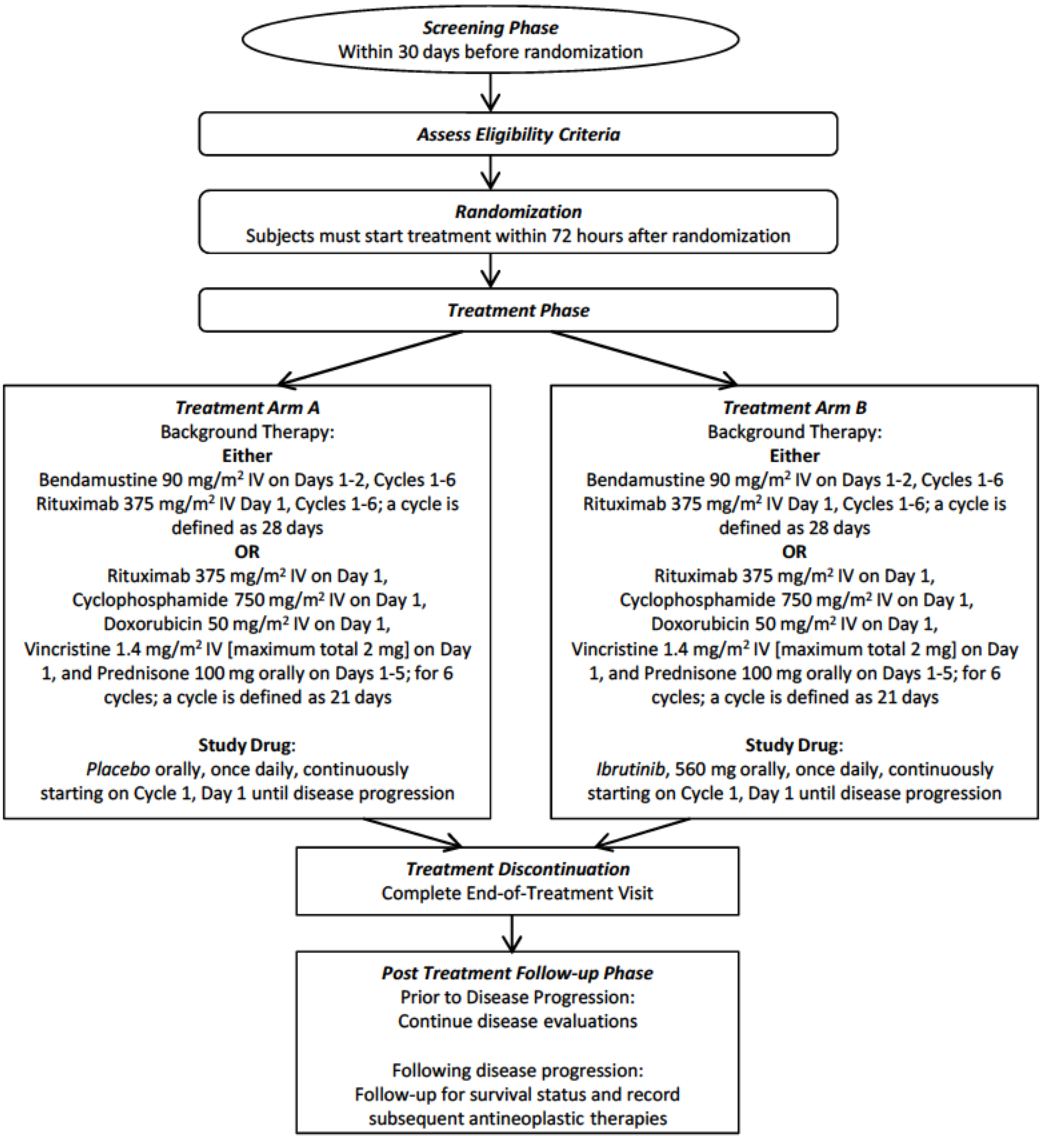
Assessment of tumor response and progression will be conducted in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). The investigator will evaluate sites of disease by radiological imaging, physical examination, or other procedures as necessary. The primary efficacy analysis of PFS will be based on investigator 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. At some visits, blood samples will be drawn for assessment of pharmacokinetic parameters and for MRD.

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 further conduct of the study (see Section 11.8). 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: Schematic Overview of the Study



3.2. Study Design Rationale

Study Population

Selection of iNHL (FL or MZL) subjects for this study was based on the promising activity seen in Phase 1 studies. An ongoing Phase 2 study (Study PCI-32765FLR2002) in chemoimmunotherapy-resistant subjects is expected to confirm the activity seen in Phase 1. While there are a number of available therapies for patients with previously treated iNHL, these agents provide limited clinical benefit to these patients, and none of these treatments are curative, highlighting the need for novel, well-tolerated, effective treatment options. Thus, there is a medical need for newer treatments that can be combined with existing therapies to provide durable clinical benefit without added toxicities.

Study Treatment

The choice of chemoimmunotherapeutic regimen used in the relapsed setting is informed by the frontline regimen used, the remission duration, and depends on the efficacy of prior regimens (Dreyling 2011). Given the increased use of bendamustine-containing regimens in frontline therapies, patients who relapse from bendamustine are commonly treated with other chemoimmunotherapeutic regimens such as R-CHOP (NCCN 2013).

A survey of treatment practices among 43 US-based community oncologists was conducted in patients with newly diagnosed FL (n=186) and relapsed FL (n=133) between 2008 and 2010 (Gregory 2010). R-CHOP was the most commonly used regimen in patients with newly diagnosed FL. An increased use of BR for the frontline treatment of FL was noted from 2008 to 2010, suggesting that community oncologists are rapidly incorporating clinical trial results into practice. Of note, there was evidence of substantial BR uptake following the landmark Rummel presentation (Rummel 2005), with 31% of those patients who initiated treatment in 2010 receiving BR compared with less than 5% of those who commenced therapy in 2008 or 2009. Rituximab monotherapy was the most common treatment in patients with relapsed FL, followed by R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), BR, and R-CHOP. The therapies that were used by these physicians in the front-line and relapsed settings broadly corresponded to published literature and were supported by treatment guidelines.

Dose Rationale

The 560 mg daily dose of ibrutinib was selected as the recommended dose in combination with BR or R-CHOP based on clinical data from Studies PCYC-04753, PCYC-1108-CA, OSU 10052, and PCI-32765DBL1002.

The pharmacokinetic and pharmacodynamic relationship between BTK active-site occupancy and ibrutinib exposure was evaluated in Study PCYC-04753. Data from Study PCYC-04753 showed that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib was adequate to sustain maximal pharmacodynamic activity for 24 hours post-dose at dose levels ≥2.5 mg/kg (191 mg). In addition, the analysis of pharmacokinetic and pharmacodynamic profiles showed that BTK active-site occupancy was saturated or near saturated (>95%) at AUC values of ≥160 ng•h/mL. In Study PCYC-04753, >85% of subjects who received

dosages ≥2.5 mg/kg/day had Day 1 area under the concentration time curve from 0 to 24 hours (AUC_{0-24}) values ≥160 ng•h/mL, indicating that the vast majority of patients who receive a dose of either 420 mg/day or 560 mg/day will achieve full BTK site occupancy. Since the pharmacokinetic of ibrutinib is highly variable, it is critical to ensure that also exposures on the lower end of the range are sufficiently high to guarantee full occupancy.

Clinical activity has been observed in FL patients in Study PCYC-04753. Of the 11 subjects with FL included in the efficacy evaluable population, 3 subjects (27%) had a best response of CR, and 2 subjects (18%) had a best response of PR, for an ORR of 45%. Median time on ibrutinib was 6.7 months (range, 0.2 to 17.1 months). Median PFS was 13.4 months. Median follow-up time was 8.8 months (range, 3.3 to 17.3 months). With the caveat of small numbers, duration of response and progression free survival subjects were favoring 5 mg/kg/day (Fowler 2012). Three subjects with MZL were also enrolled, with 1 PR noted. The median PFS for all 3 subjects was 7 months (95% CI: 2 to 9 months).

The safety profile of 560 mg dosing in combination with BR or R-CHOP is acceptable. In a phase 1 study where Ibrutinib at a dose of 560 was combined with BR no DLTs were observed (Blum 2012). During a dose escalation study of ibrutinib (280, 420, and 560 mg) in combination with R-CHOP, DLTs were observed at different dose levels, however, MTD was not reached (DBL1002). The Study Evaluation Team recommended 560 mg ibrutinib + R-CHOP for evaluation in Phase 2.

Based on these data and for consistency across the lymphoma program, the 560 mg dose has been selected for this study.

The assessment of pharmacokinetics is important in understanding both safety and efficacy in this patient population. 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 determination of subject-covariates that influence the pharmacokinetics of the drug, this may provide supportive evidence for the efficacy and safety analyses, help in deriving dosing regimens not directly studied in clinical studies, and identify at-risk subjects who require a dose-adaptation.

Blinding, Control, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. 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 clinical endpoints. Subjects will be stratified by (1) background chemoimmunotherapy treatment, (2) refractory versus relapsed disease, (3) iNHL histology, and (4) number of prior lines of therapy (for definitions see Section 11.3.1).

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 30 days before randomization. Computed tomography/magnetic resonance imaging (CT/MRI), positron emission tomography (PET), and bone marrow aspirate/biopsy may be performed up to 60 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. Waivers to the protocol inclusion and exclusion criteria will not be granted. Investigators must ensure that all inclusion and exclusion criteria have been satisfied at screening. Retesting during the Screening Period is allowed. A subject is considered eligible if the last observation before randomization satisfies the inclusion and exclusion criteria. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before obtaining randomization for a subject in the study.

Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Subject must be 18 years of age or older (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Criterion modified per Amendment INT-1:

   2.1 Have both of the following

   - Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to the following at initial diagnosis and without evidence of pathological transformation or clinical signs suggesting transformation
     a. follicular lymphoma (FL) Grade 1, 2, or 3a
     b. marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)
   - Prior to randomization, diagnosis must be confirmed by review of local pathology report. If report from local laboratory is not available or insufficient, diagnosis must be confirmed by central pathology laboratory, as described in Section 9.1.2.

3 Criterion modified per Amendment INT-1:

   3.1 At least 1 prior treatment with a CD20 antibody combination chemoimmunotherapy regimen

4 Criterion modified per Amendment INT-1:

4.1 Disease that has relapsed or was refractory after prior chemoimmunotherapy. Refractory disease is defined as failing to achieve PR or better after the most recent treatment.

5. At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma (Cheson 2007) (ie, 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).

6. Eastern Cooperative Oncology Group performance status grade 0 or 1.

7. Criterion modified per Amendment INT-1:

7.1 Hematology values must be within the following limits:

a. absolute neutrophil count (ANC) ≥1,500/μL independent of growth factor support

b. platelets ≥100,000/μL or ≥50,000/μL if bone marrow involvement independent of transfusion support

8. 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 creatinine clearance (C_{Cr}) ≥30 mL/min/1.73m^2 (please refer to Attachment 3)

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. For females, these restrictions apply for 6 months after the last dose of bendamustine, 12 months after the last dose of rituximab or 1 month after the last dose of study medication, whichever is later. Men must also agree not to donate sperm during and after the study. 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 medication, whichever is later.

10. Women of childbearing potential must have a negative serum (β-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 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. Prior nitrosoureas within 6 weeks, other chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 4 weeks of randomization.

2. Prior treatment with ibrutinib or other BTK inhibitors. Subjects who progressed or become refractory while on treatment with phosphoinositide 3-kinase (PI3K) inhibitors are excluded. However, subjects who are responding to PI3K inhibitors but had treatment discontinued due to toxicity, or subjects who relapsed after stopping PI3K treatment, are eligible.

3. Received a prior allogeneic hematopoietic stem cell transplant. Prior autologous hematopoietic stem cell transplant is allowed.

4. Unable to receive either BR or R-CHOP background chemotherapy, based on prior treatment history and cardiac function. Refer to Figure 2.

5. Known CNS lymphoma.

6. Diagnosed or treated for malignancy other than iNHL (FL or MZL), 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 carcinoma in situ without evidence of disease

7. History of stroke or intracranial hemorrhage within 6 months prior to randomization.

8. Requires anticoagulation with warfarin or equivalent Vitamin K antagonists (eg, phenprocoumon).

9. Criterion modified per Amendment INT-1:

    9.1 Requires treatment with strong CYP3A inhibitors (see Section 8.1)

10. 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.

    a. subjects receiving R-CHOP are excluded if left ventricular ejection fraction is below institutional normal limits

11. Vaccinated with live, attenuated vaccines within 4 weeks of randomization.

12. Criterion modified per Amendment INT-1:

    12.1 Known history of human immunodeficiency virus (HIV) or active Hepatitis C virus (HCV; RNA polymerase chain reaction [PCR]-positive) or active Hepatitis B virus (HBV; DNA PCR-positive) infection or any uncontrolled active systemic infection requiring IV antibiotics (see Section 9.5). Subjects with PCR-negative HBV are permitted in the study.

13. Known anaphylaxis or immunoglobulin E (IgE)-mediated hypersensitivity to murine proteins or to any component of rituximab including polysorbate 80 and sodium citrate dehydrate.

14. 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.

15. Received investigational agents within 4 weeks prior to randomization or concurrent enrollment in another therapeutic investigational clinical treatment study.

4.3. Prohibitions and Restrictions

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. 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 (1) background chemotherapy treatment, (2) refractory versus relapsed disease, (3) iNHL histology, and (4) number of prior lines of therapy (for definitions see Section 11.3.1). The sponsor will strive towards an adequate number of subjects randomized into either of the background chemotherapy regimens. 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

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 concentration) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can 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 case report form (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.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. After treatment is unblinded, subjects assigned to ibrutinib will continue to receive open-label study drug; placebo will be discontinued.

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

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).

6. DOSAGE AND ADMINISTRATION

6.1. Study Treatment

Study Drug

Subjects will be randomized in a 1:1 ratio to either Treatment Arm A or Treatment Arm B. Treatment with the study drug will start on Study Day 1 and 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 every day along with background chemotherapy.

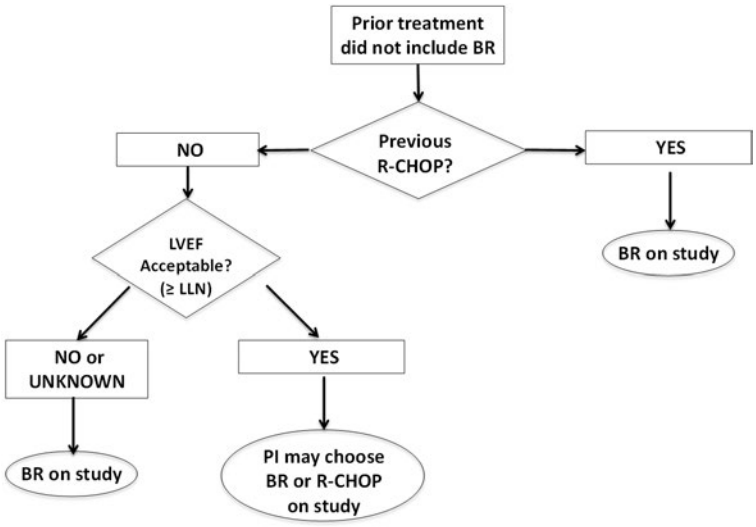
Treatment Arm B:

560 mg (4 x 140-mg capsules) of ibrutinib will be administered orally once daily every day along with background chemotherapy.

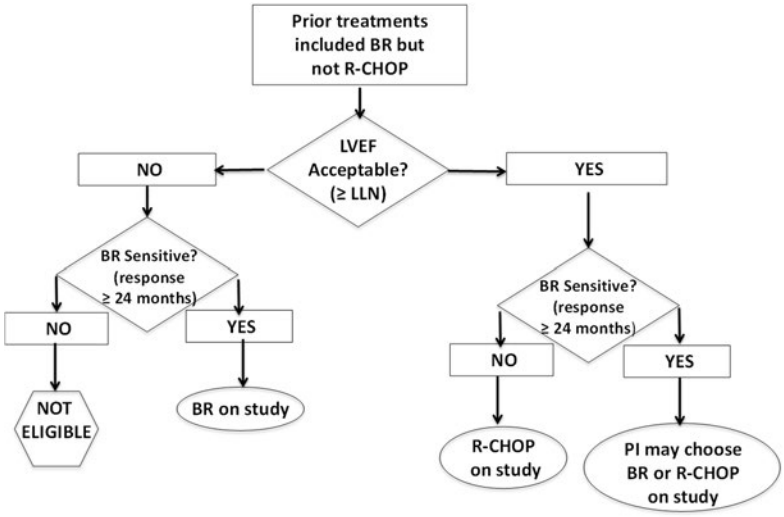
In Treatment Arm A and Treatment Arm B, subjects will receive either BR or R-CHOP as the background therapy for 6 cycles unless progression of disease or unacceptable toxicity is encountered prior to Cycle 6. Background therapy will be determined based on prior treatment history and cardiac function, as outlined in Figure 2. Once the background therapy regimen has been selected, subjects may not be switched to the other regimen. "BR sensitive" is defined as response lasting ≥24 months from the start of treatment to relapse.

Figure 2: Background Chemotherapy Decision Tree

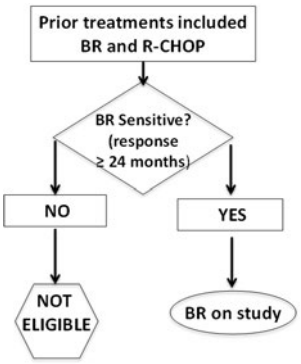
A.



B.



C.



BR=bendamustine and rituximab; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; PI=principal investigator; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

In order to achieve an adequate balance between the background chemotherapy treatments, the sponsor will strive towards an adequate number of subjects randomized into either of the background chemotherapy regimens.

BR regimen (28 day cycles):

- bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of Cycles 1 to 6
- rituximab 375 mg/m^2 IV on Day 1 of Cycles 1 to 6

R-CHOP regimen (21 day cycles):

- rituximab 375 mg/m^2 IV on Day 1 of Cycles 1 to 6
- cyclophosphamide 750 mg/ m^2 IV on Day 1 of Cycles 1 to 6
- doxorubicin 50 mg/m^2 IV on Day 1 of Cycles 1 to 6
- vincristine 1.4 mg/m^2 IV [maximum total 2 mg] on Day 1 of Cycles 1 to 6
- prednisone 100 mg orally on Days 1 to 5 of Cycles 1 to 6

Note: In either regimen, rituximab may be administered separately on Day 1, followed by the remaining intravenous chemotherapy drugs on Day 2 (and Day 3 for bendamustine), at the investigator's discretion.

6.2. BR Administration

Investigators should refer to the package inserts for the storage and handling, and detailed instructions on the administration of bendamustine hydrochloride and rituximab, respectively. BR is administered IV, per institutional standards, at the dosages described above in Section 6.1.

Doses of bendamustine hydrochloride and rituximab should be reduced or held in accordance with the dose modification guidelines in the respective product labels, as described below.

6.2.1. Bendamustine Hydrochloride Dose Modifications

Bendamustine hydrochloride administration should be delayed in the event of 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 hematologic events, bendamustine hydrochloride may be reinitiated after blood counts have improved (ANC ≥1 x 10^9/L [≥1,000/µL]; platelets ≥75 x 10^9/L [≥75,000/µL]), at the discretion of the investigator.

In addition, dose reduction may be warranted as follows:

- Dose modifications for Grade 4 hematologic toxicity: the dose should be reduced to 60 mg/m^2 on Days 1 and 2 of each cycle. If Grade 4 toxicity recurs, the dose should be reduced to 45 mg/m2 on Days 1 and 2 of each cycle.

- Dose modifications for clinically significant Grade ≥3 non-hematologic toxicity: the dose should be reduced to 60 mg/m^2 on Days 1 and 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.

6.2.2. Rituximab Dose Modifications

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 should be held for any Grade 4 toxicity or for any rituximab-related, clinically significant, unmanageable Grade 3 adverse events. Rituximab may be held for a maximum of 28 consecutive days for a drug-related toxicity. Discontinue rituximab permanently if it cannot be restarted within 28 days due to drug-related toxicity. If rituximab is discontinued for toxicity, treatment with bendamustine hydrochloride and/or ibrutinib or placebo may be continued.

6.3. R-CHOP Administration

Investigators should refer to the local prescribing information for storage and handling, and detailed instructions on the administration of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (or equivalent). Rituximab biosimilar drugs are not permitted in this study. All IV drugs should be administered per institutional standards at the dosages described above in Section 6.1. Refer also to the study Investigational Product Procedures Manual.

6.3.1. Rituximab Dose Modifications

Please refer to Section 6.2.2.

6.3.2. Cyclophosphamide Dose Modifications

Dose adjustments for cyclophosphamide must follow the provided prescribing information. The most common adverse events experienced with cyclophosphamide are hematological toxicities; myelosuppression with leucopenia, anemia, and thrombocytopenia may occur. The lowest leukocyte and platelet levels occur in the first to second week after treatment is started. Recovery usually occurs within 3 to 4 weeks after treatment is started. Following treatment with cyclophosphamide, hemorrhagic cystitis and hematuria can occur. These may necessitate interruption of dosing.

To start a cycle with cyclophosphamide, ANC must be ≥1,000/μL and platelets ≥75,000/μL. The cycle may be delayed up to 2 weeks until the above values are documented on Day 1 of the cycle. Subjects who develop hematological toxicities thought to be causally related to cyclophosphamide must have their dose adjusted on Day 1 of the subsequent cycle according to Table 4.

Table 4: Dose Modification for Cyclophosphamide and Doxorubicin for Hematological Toxicities

ANC and Neutropenia [µL] (any time during cycle)	Platelet count [µL][a]	Dose Given (on next cycle)
≥1,000/µL	>75,000/µL	100% of the designated dose
>500/µL and no febrile neutropenia	>50,000/µL	100% of the designated dose after recovery of ANC to 1,500/µL and platelets to 100,000/µL
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C)	N/A	Initiate G-CSF for all subsequent cycles
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors	<50,000/µL	25% dose reduction for subsequent cycles
Recurrence of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors	Recurrence of <50,000/µL	Additional 25% dose reduction for subsequent cycles
Third episode of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors and 2 dose reductions	Third episode of <50,000/µL	Discontinue

ANC=absolute neutrophil count; G-CSF=granulocyte colony stimulating factor; N/A=not applicable

[a] Dose reductions due to low platelet counts are not required in subjects with thrombocytopenia due to bone marrow infiltration from lymphoma who entered the study with platelet counts <75,000/µL.

6.3.3. Doxorubicin Dose Modifications

Dose adjustments for doxorubicin must follow the provided prescribing information. The recommended lifetime cumulative dose limit of doxorubicin is 450 to 550 mg/m^2. The maximum dose given for each subject in this study will be 300 to 400 mg/m^2, depending on the number of cycles given.

Dose-limiting toxicities of doxorubicin therapy are mucositis, myelosuppression, and cardiotoxicity. Myelosuppression includes leucopenia, thrombocytopenia, and anemia, reaching nadir at 10 to 14 days after treatment. Cardiotoxicity includes arrhythmia that may occur directly after administration and ECG changes may last up to 2 weeks after administration. Cardiotoxicity may, however, occur several weeks or months after administration.

Doxorubicin is metabolized by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity. Doxorubicin dosage must be reduced if hepatic function is impaired according to Table 5:

Table 5: Dose Modification of Doxorubicin for Hepatic Function Impairment

Serum Bilirubin Levels	Recommended Dose
2.0–3.0 mg/dL	50% normal dose
>3.0 mg/dL	25% normal dose

These dose reductions are not required in subjects with Gilbert syndrome and in cases where the increase of bilirubin is due to non-hepatic reasons. Dose reductions due to hematological toxicities should be performed as indicated in Table 4.

6.3.4. Vincristine Dose Modifications

Dose adjustments for vincristine must follow the provided prescribing information. The vincristine dosage must be reduced if hepatic function is impaired according to Table 6:

Table 6: Dose Modification for Vincristine Hepatic Function Impairment

Serum Bilirubin Levels	Recommended Dose
2.0–3.0 mg/dL	75% normal dose
>3.0 mg/dL	50% normal dose

Vincristine doses should be re-escalated when hyperbilirubinemia improves. These dose reductions are not required in subjects with Gilbert syndrome and in cases where the increase of bilirubin is due to non-hepatic reasons.

Neurologic toxicity is the most common adverse event experienced with vincristine and is related to dose and age. In case of severe neurotoxicity (Grade 3), vincristine should not be administered, especially if there are signs of paresthesia or paresis. Treatment may be resumed at 50% of the dose when symptoms subside. Vincristine should be reduced by 25% for any episode of ileus/constipation requiring hospitalization. Vincristine should be permanently discontinued for Grade 4 neuropathy of any type.

6.3.5. Prednisone (or Equivalent) Dose Modifications

Dose adjustments for prednisone (or equivalent) must follow the provided prescribing information. In regions where prednisone is not marketed or available, prednisolone will be used. By definition, high-dose prednisone or equivalent will be used in this study at 100 mg. Subjects administered high-dose prednisone or equivalent should be monitored carefully as there is a relatively higher risk of developing or exacerbating some conditions (eg, bacterial infections, viral infections, systemic mycoses, hypertension, diabetes mellitus, and gastrointestinal conditions such as peptic ulcers, pancreatitis, and diverticulitis).

In the event that a subject develops an adverse event related to prednisone or equivalent and is not able to tolerate 100 mg as required per protocol, the dose should be adjusted to a level specific to that subject but should be no less than 80 mg per day (so that the subject still receives a high dose of prednisone [or equivalent]). In exceptional circumstances, a subject may not tolerate sudden steroid withdrawal after 5 days of prednisone or equivalent therapy. In such an instance, a tapering regimen of prednisone (or equivalent) is indicated.

6.4. Delay of Chemotherapy

The start of a new cycle may be delayed on a weekly basis until recovery of toxicity to a level allowing continuation of therapy. A subject whose cycle is delayed should be assessed weekly for resolution of toxicity. It is not always easy to assess the role of any 1 agent in these events; therefore, it is at the investigators discretion to decide if 1 or more agents are responsible and take action as described in Section 6.2 through Section 6.3. If toxicity persists after a 2-week cycle delay, that is related to 1 specific chemoimmunotherapy drug (eg, bendamustine, doxorubicin,

etc.), the offending drug should continue to be withheld and the new cycle should be started with the remaining drugs. If chemotherapy is delayed, treatment with study drug should be continued during the delay phase unless criteria for stopping study drug are also met (see Section 6.5). If there is a delay in the start of a new cycle of more than 28 days due to insufficient recovery from toxicity (with all chemoimmunotherapy drugs withheld), subjects will permanently discontinue chemoimmunotherapy. However, the start of a new cycle after more than a 4-week delay (with all drugs withheld) may occur if there is clear clinical benefit and only after approval by the sponsor. Subjects who discontinue chemoimmunotherapy without disease progression will continue study drug until disease progression or unacceptable toxicity.

The following parameters must be met on the first day of each cycle of chemotherapy (other than Cycle 1):

- platelet count ≥75,000 cells/μL (prior platelet transfusion is allowed)
- subjects with thrombocytopenia due to bone marrow infiltration from lymphoma are allowed to have ≥50,000 cells/μL on the first day of the cycle
- hemoglobin ≥8 g/dL (≥4.96 mmol/L) (prior red blood cell transfusion or recombinant human erythropoietin use is allowed)
- ANC ≥1,000 cells/μL (growth factor use is allowed, eg, granulocyte colony stimulating factor or granulocyte-macrophage colony-stimulating factor)

6.5. Study Drug Administration

Ibrutinib (4 capsules for a dose of 560 mg) or placebo should be administered orally with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. Avoid grapefruit and Seville oranges with ibrutinib treatment. Ibrutinib administration should continue until disease progression or until no longer tolerated by the subject. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

One bottle of study drug will be administered at Cycles 1 to 6. Subjects will return in 3 or 4 weeks for their Cycle 7 visit. Starting at Cycle 7, 2 bottles of study drug will be administered. Post-chemotherapy period visits (dispensing of study drug, safety assessments, and clinical lab assessments) can occur earlier to align with efficacy assessments. At each study visit, sufficient study drug required for treatment until the next visit should be dispensed. Unused study drug dispensed during previous visits must be returned and drug accountability records updated. Returned capsules cannot 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.

6.5.1. Study Drug (Ibrutinib or Placebo) Dose Modifications

Treatment with study drug should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Study drug may be held for a maximum of 28 consecutive days for drug-related toxicity. Study drug should be discontinued permanently in the event of a

drug-related toxicity lasting more than 28 days. 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. Changes must be recorded in the Dosage Administration page of the CRF.

The below actions in Table 7 and Table 8 should be taken for the following drug related toxicities:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC <0.5 x 10^9/L [ie, <500/μL]) for >14 days
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/μL]) in the presence of significant bleeding
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L [ie, <25,000/μL])
- Grade 3 or greater non-hematological toxicity (noting specific Table 8 recommendations for Grade 3 or higher cardiac failure and cardiac arrhythmias).
- Grade 2 cardiac failure (Table 8)
- Any other Grade 4 or unmanageable Grade 3 hematological toxicity.

Table 7: Ibrutinib / Placebo Dose Modifications for Ibrutinib Toxicities for Events not Specified in Table 8

Occurrence	Action
First	Hold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level[a]
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

a. When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.

Table 8: Ibrutinib / Placebo Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Events	Occurrence	Action
Grade 2 cardiac failure	First	Hold study drug until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])
	Second	Hold study drug until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])
	Third	Discontinue study drug
Grade 3 cardiac arrhythmias	First	Hold study drug until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])[a]
	Second	Discontinue study drug
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue study drug

a. Evaluate the benefit-risk before resuming treatment.

7. TREATMENT COMPLIANCE

The study drug 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. Administration of the study drug must be recorded in the subject's source documents. The study drugs may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

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 pharmacy manual/study site investigational product manual.

8. CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study beginning with signing of informed consent to 30 days after the last dose of study drug. All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and indication.

8.1. Concomitant Medications to be used with Caution

Concomitant Use of Ibrutinib /Placebo and CYP3A Inhibitors/Inducers Drugs

Ibrutinib is metabolized primarily by CYP3A (Section 1.3.1). Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A inhibitors should be avoided.

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased exposure (C_{max} and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in patients with B-cell malignancies, co-administration of voriconazole increased C_{max} and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, 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. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in Table 9. All other strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see recommended dose modifications in the table below. In patients with B-cell malignancies, co-administration of CYP3A inhibitor erythromycin increased C_{max} and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (eg, fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce the dose as per recommended dose modifications in Table 9. 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.

Table 9: Dose Modifications for Ibrutinib for Subjects Receiving Concomitant CYP3A Inhibitors

Co-administered Drug	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use** [a]
• Mild CYP3A inhibitors	No dose adjustment required
• Moderate CYP3A inhibitors	280 mg once daily
• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily
• Other strong CYP3A inhibitors • Posaconazole at higher doses [b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as antiinfectives for 7 days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than 7 days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

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

Key: BID = twice a day; CYP = cytochrome P450.

Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreases ibrutinib plasma concentrations 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 and https://medicine.iu.edu/internal-medicine/specialties/clinical-pharmacology/drug-interaction-flockhart-table.

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

Concomitant Use of QT Prolonging Agents

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

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. Consultation with the sponsor's Medical Monitor is recommended. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

8.2. Prohibited Concomitant Medications

Any concurrent chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited.

Corticosteroids are allowed when used to premedicate or manage rituximab infusion-related reactions or contrast allergies, as well as short courses (<14 days) of corticosteroid treatment for non-cancer related medical reasons (ie, treatment for autoimmune cytopenias) at doses not to exceed 100 mg/day of prednisone or equivalent. Otherwise, corticosteroid dosages equivalent to prednisone >20 mg/day are not permitted; routine infusion premedication with corticosteroid doses of >100 mg IV prednisolone (or equivalent) is also not permitted.

8.3. Medications Permitted During Treatment

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted, including pre-medication for rituximab and bendamustine infusions per the rituximab and bendamustine package inserts, respectively. Prophylaxis for tumor lysis syndrome may be administered to subjects considered to be at risk. Use of neutrophil growth factors (filgrastim and pegfilgrastim) are permitted per the ASCO guidelines or according to the institution's guidelines (Ozer 2000). Use of anti-microbial prophylaxis (eg, pneumocystis pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent), according to the institution's guidelines, is recommended. Hepatitis B surface antigen positive subjects should receive appropriate prophylaxis according to local standards (eg, lamivudine).

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, biomarker, PROs, and safety measurements applicable to this study.

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

Total blood volume for the study is approximately 20 mL for clinical laboratory assessments at the start of each cycle of chemotherapy and 15 mL every 8 weeks thereafter plus 20 mL at the End-of-Treatment (EOT) and every 12 weeks in Follow-up prior to PD, 20 mL for pharmacokinetics in Cycles 1 and 2 plus 2 mL in Cycle 3, and 2 mL for pregnancy testing at screening [for women of childbearing potential only]).

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

9.1.2. Screening Phase

All subjects must sign an informed consent form (ICF) prior to the conduct of any study-related procedures. During this phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event Schedule. Screening procedures will be performed up to 30 days (60 days for CT, MRI, PET, and bone marrow biopsy and aspirate) before randomization. Laboratory tests noted in the inclusion criteria must be within the limits specified prior to randomization. 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.

During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. This evaluation will include a complete medical history, including confirmation of iNHL (FL or MZL) diagnosis (based on paraffin embedded biopsy tissue block or slides, preferably of lymph node origin), and relevant laboratory reports, key features of disease, and prior cancer therapy. The subject's baseline cardiovascular status will be assessed by an ECG.

Subjects will be required to have confirmation of disease (FL or MZL) prior to randomization. A report from the local laboratory may be acceptable to demonstrate diagnosis of FL or MZL and must be sent to the central laboratory and the sponsor for review and confirmation of the diagnosis. For subjects who do not have this report available or the report is deemed not acceptable by the central laboratory, a tumor tissue block or slides must be sent to the central laboratory and confirmation of iNHL (FL or MZL) diagnosis must be obtained from the central laboratory prior to randomization.

For subjects with MZL, if diagnosis was approved based on the local pathology report, a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained slides must still be sent to the central laboratory after randomization for central confirmation of the diagnosis.

For subjects with FL, if diagnosis is determined from review of the local pathology report, a minimum of 5 unstained slides, sectioned at a thickness of 5 μm, must still be sent to the central laboratory for MRD analysis.

The screening bone marrow biopsy will be obtained to document bone marrow involvement with lymphoma and does not need to be shipped to the central laboratory.

9.1.3. Treatment Phase

The Treatment Phase will begin at randomization and will continue until study drug discontinuation due to disease progression, or unacceptable toxicity, whichever occurs first. Subjects should start study drug treatment within 72 hours after randomization. The last measurements taken on Day 1 of Cycle 1 before administration of study drugs or at screening (whichever value was last) will be defined as the baseline values for safety assessments and

treatment decisions. Laboratory values that are obtained prior to Cycle 1, Day 1 should be repeated if they were collected more than 5 days prior to the start of study drug (ibrutinib or placebo). These values should be consistent with the values in the inclusion and exclusion criteria in order for the subject to receive treatment.

The FACT-Lym and EQ-5D-5L will be collected at the beginning of the clinic visits, preferably, before any procedures or physician interactions. After the PRO questionnaires have been administered, a symptom-directed physical examination (including lymphoma B symptoms and ocular changes) will be conducted (see Section 9.5). Laboratory testing scheduled for the same visit should be conducted preferably, after the PRO questionnaires have been administered. Adverse events and changes to concomitant medications will be recorded. Subjects will be evaluated throughout this phase for possible toxicities. Dose modifications will be made as according to criteria described in the protocol (see Section 6.2, 6.3, and 6.5.1).

Adverse events and changes to concomitant medications will be recorded. Subjects will be evaluated throughout this phase for possible toxicities. Dose modifications will be made as according to criteria described in the protocol (see Section 6).

All subjects will visit the study site on Day 1 of the first 6 cycles. Subjects receiving BR will return on Day 2 of the first 6 cycles to receive bendamustine. Each cycle is 28 days for BR and 21 days for R-CHOP. When all evaluations have been completed at each of these visits, and it has been determined that the subject may continue to receive treatment, chemoimmunotherapy with either BR or R-CHOP will be administered IV and 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. After the end of chemotherapy, clinic visits for study-related procedures will occur every 8 weeks. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If a subject shows signs of progression on physical examination or laboratory assessment, the subject may continue study treatment until progression is confirmed by CT scan. If progressive disease is diagnosed, then the subject will discontinue study drug, complete the End-of-Treatment Visit within 30 days after the last dose of study drug, and enter the Posttreatment Follow-up Phase.

End of Treatment

An EOT Visit will be scheduled within 30 days after the last dose of study drug 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 progression, adverse event, or other reasons and enter the Posttreatment Follow-up Phase should have the EOT Visit completed before starting any subsequent anti-lymphoma treatment. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect adverse events that occur within 30 days after the last dose of study drug.

9.1.4. Posttreatment Phase (Follow-Up)

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

Progression-free survival is the primary endpoint for this study. Therefore, for subjects who discontinue treatment prior to disease progression, it is imperative that the regularly scheduled disease assessments are performed throughout the Posttreatment Follow-up Phase until disease progression, death, or study end, whichever occurs first, as outlined in Section 9.2.1. Evidence of disease progression should be done in accordance with the Revised Response Criteria for Malignant Lymphoma and it has to be documented at the time at which it is first detected (Cheson 2007).

For all subjects who reach progression, the sponsor medical monitor should be notified within 24 hours of the investigator becoming aware of the progression. Progression needs to be confirmed by the sponsor medical monitor before subsequent therapy is started. Following disease progression, contact will be made to determine survival status and subsequent antineoplastic therapy every 24 weeks until death, lost to follow-up, withdrawal of consent, or study end. 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.

Following disease progression, the PROs will be performed once after approximately 24 weeks. Subjects who visit the site for the follow-up assessments should complete the PRO questionnaires at that time. If the PROs are 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 questionnaires. If the subject is unable to complete the PROs during the Post-treatment Phase, the reason for not completing the questionnaire will be documented (ie, too ill, subject refused).

9.1.5. Clinical Cutoffs

Three clinical cutoffs are planned. The first 2 clinical cutoffs will occur when approximately 151 and 252 PFS events have been observed, respectively. The interim analysis and the primary analysis (ie, final analysis of the primary endpoint PFS) will take place at these 2 clinical cutoffs, respectively; subject treatment assignment will be unblinded and placebo treatment will be stopped at the primary analysis. The last cutoff will occur at the time of the end of study, when approximately 50% of the randomized subjects have died or the sponsor terminates the study, whichever comes first. The end of study clinical cutoff is chosen to ensure reasonable maturity of the survival data and allow estimation of median OS. Investigators will be informed when the clinical cutoffs are to occur.

The Time and Events Schedule after clinical cutoff for the primary analysis is shown in Table 2. The following data will continue to be collected for all subjects after the clinical cutoff for the primary analysis survival data, best response and progressive disease on subsequent anti-lymphoma therapy, and reports of new malignancies. Subjects without progressive disease will continue to have disease assessments according to standard of care, until disease progression. In addition, the following data will be collected for subjects still receiving study treatment after the clinical cutoff for the primary analysis: study drug administration, adverse events during treatment and within 30 days after last dose that are either serious, Grade ≥3 or result in dose

interruption, reduction, or discontinuation; major hemorrhages (see Section 12.3.3.1), new malignancies of any grade; concomitant medications associated with a serious adverse event, and laboratory assessments and vital signs indicative of the onset and recovery from an adverse event. Where allowed by local law, public records may be used to document death for the purpose of obtaining survival status.

9.2. Efficacy

9.2.1. Evaluations

Eligible subjects must have at least 1 measurable site of disease by radiological assessment (Cheson 2007). Efficacy evaluations will be conducted as specified in the Time and Events Schedule (Table 1 and Table 2) and may include the following: CT scans, MRI, PET using [^{18}F]-fluorodeoxyglucose (FDG), bone marrow aspirate and biopsy, physical examination including lymphoma B symptoms, or 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. Subject lymphoma related symptoms and concerns will be measured by the lymphoma subscale of the FACT-Lym and health status will be measured by the EQ-5D-5L.

9.2.1.1. Radiographic Image Assessments (CT/MRI)

Efficacy assessments with CT scans with IV contrast of the neck (full neck views must be obtained), chest, abdomen, and pelvis and any other location where disease was present at Screening will be performed at every evaluation. Subjects who are intolerant of IV CT contrast agents will have CT scans performed with oral contrast. Contrast is required unless otherwise contraindicated. 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; however, the CT scanning must be done according to the imaging requirements provided to the radiologist in the radiology manual to ensure that an optimized CT 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 neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required only if clinically indicated.

Radiological assessments will be performed at Screening, Week 12, Week 24, and then every 16 weeks for 3 years, thereafter every 24 weeks (±7-day window for all assessments) until disease progression, death, or the clinical cutoff for the final analysis of the primary endpoint, whichever comes first. Assessments should be scheduled on a calendar basis; interruptions of treatment will not affect when scans are obtained. 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 until disease progression, death, or clinical cutoff for the final analysis of the primary endpoint, whichever occurs first.

9.2.1.2. Positron Emission Tomography (PET Scan)

Whole body FDG-PET scan (skull base to the proximal femur) will be performed at screening and at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction).

Assessment of PET results is based on published criteria (Juweid 2007). 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 start of treatment must have a repeat bone marrow evaluation (ie, bone morrow aspirate and biopsy) at the time of CR (preferably within 30 days of the initial documentation of CR). If bone marrow involvement is confirmed with morphology, immunohistochemistry does not need to be performed.

9.2.1.4. Fluid Aspiration at Other Sites of Disease

If diagnosis of disease progression is based solely on sites of disease with fluid accumulation (ascites, pleural or pericardial effusions), a diagnostic sample of fluid must be obtained and cytology or flow cytometry confirmation of the presence of lymphoma is required.

9.2.1.5. Physical Examination

During the Screening, Treatment, and Posttreatment Follow-up Phases (see Time and Event Schedules for exact procedures), subjects should have physical examinations to evaluate possible presence of palpable lymph nodes, tumor masses, or enlargement of spleen and liver. Symptom-directed questions will be asked to evaluate for presence of B-symptoms.

9.2.1.6. Patient-Reported Outcomes

Two PRO instruments, the lymphoma subscale of the FACT-Lym and EQ-5D-5L, will be administered up to the clinical cutoff for the primary analysis, at the timepoints specified in Table 1 of the Time and Events Schedule; no PROs will be assessed after clinical cutoff for primary analysis (Table 2). The FACT-Lym (Attachment 1) was originally developed to assess functional status and well-being of patients with NHL (Eremenco 2004). The lymphoma scale of the FACT-Lym includes 15 items and scores range from 0 to 60, with each item scored on a 5-point scale from 0 (not at all) to 4 (very much). Higher scores represent better health status with respect to fewer disease related symptoms and fewer disease related concerns of patients. In patients with FL, the lymphoma subscale has been shown to differ according to disease state. Patients who have

relapsed disease report more disease-related symptoms and concerns than patients who are either newly diagnosed, in partial or complete remission, or completely disease free (Pettengell 2008). Carter et al (2008) and Cella et al (2005) reported a minimal important change score for the Lym subscale in a relapsed/refractory MCL population ranges 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.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (Attachment 2). 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 (Rabin 2011). For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness 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). The scores for the 5 separate questions are categorical and should not be analyzed as cardinal numbers. However, 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.

9.2.2. 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 are progression-free and alive or have unknown status will be censored at the last tumor assessment.

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.
- Duration of response (CR or PR) is defined as duration 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. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Time to worsening (TTW) in the Lym subscale of the FACT-Lym is defined as the time from the date of randomization to the start date of the worsening of patient symptoms. Worsening is defined by a 5-point decrease from baseline in patient symptoms.
- Safety parameters of ibrutinib when combined with either BR or R-CHOP.

Exploratory Endpoints

- Time-to-next treatment is measured from the date of randomization to the start date of any anti-lymphoma treatment subsequent to the study treatment. Subjects without subsequent treatment will be censored at the date of the last site visit.
- Minimal residual disease negative rate is defined as the proportion of FL subjects who reach MRD-negative disease status.
- The mean change from baseline in EQ-5D-5L scores for each post baseline assessment.
- Frequency of biomarkers associated with resistance to ibrutinib in subjects who develop resistance compared to those who respond
- Pharmacokinetic parameters (eg, oral plasma clearance, oral volume of distribution at steady state) or metrics of systemic exposure (eg, AUC, minimum observed serum concentration) of ibrutinib after oral daily dosing. Parameters describing the potential relationships between ibrutinib metrics of exposure with relevant clinical, or biomarker information.

9.2.3. Efficacy Criteria

9.2.3.1. Assessment of Disease Response and Progressive Disease

Disease evaluations, for the purpose of the study result analyses, will be performed by the investigators according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). All efficacy assessments must continue until disease progression (even if subsequent therapy is started), withdrawal of consent from study participation, or clinical cutoff for final analysis of the primary endpoint PFS. For all subjects with disease progression, the sponsor medical monitor should be notified within 24 hours of the investigator becoming aware of the progression. Progression needs to be confirmed by the sponsor medical monitor before subsequent therapy is started.

9.2.3.2. Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease by radiological assessment. 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 gastrointestinal 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.

9.2.3.3. Response Categories

The response categories being used to assess efficacy are based on the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

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 gastrointestinal 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 the appearance of any of the criteria noted below:

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 lymphoma 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) cytologic confirmation of the presence of lymphoma is required.

9.3. Pharmacokinetics

9.3.1. Evaluations

In both treatment arms, blood samples will be collected from all subjects for determination of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant) according to the Time and Events Schedule. These sparse samples will be used for the development of a population-based pharmacokinetic model.

Subjects should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until instructed to do so at the site. Subjects 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, area under the plasma concentration-time curve 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 and Minimal Residual Disease

Blood samples for biomarker evaluations will be collected from all subjects on Day 1 of Cycle 1, Day 1 of Cycle 2 and at the time of suspected disease progression, preferably within 24 to 48 hours of the last dose of ibrutinib, or the EOT Visit for subjects who discontinue treatment without disease progression.

A portion of the FFPE tissue block or slides collected for confirmation of disease for FL subjects prior to randomization may be used for central assessment of MRD and for biomarker analyses. If the FFPE tissue block or slides were not needed for confirmation of diagnosis, additional tissue or slides will need to be sent to the central laboratory for MRD analysis. For subjects with FL, blood

samples for MRD will be collected on Day 1 of Cycle 1. For those subjects with FL who have achieved CR, blood samples will be collected at subsequent scheduled disease assessment visits for assessment of MRD (see Time and Events Schedule Table 1) until clinical cutoff for the primary analysis. Thereafter samples will no longer be collected for MRD analysis (Table 2). A portion of the bone marrow sample collected to confirm CR may be assessed for MRD, if available.

Current technologies, designed to identify and track patient-specific B-cell clones, will be used to assess MRD. Specific amplification and sequencing of the CDR3 region of the B-cell receptor affords identification (over-represented clones at baseline) and sensitive tracking (post-treatment) of a patient's specific clones. 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 PCR (qRT-PCR), gene expression profiling, microRNA (miRNA), methylation, mutational and RNA sequencing (RNASeq) analyses, or other similar technologies utilized for analysis of ribonucleic acid (RNA) or somatic deoxyribonucleic acid (DNA) analysis. The blood samples may also be used for secreted protein or flow cytometry analyses to characterize immune response changes to the treatment. Genes identified in previous studies with ibrutinib will 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.

Biomarker and MRD analyses are dependent on the availability of appropriate assays and clinical response rates. Samples will be collected only at sites where local regulations and shipping logistics permit. 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 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 data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a 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.

9.5. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Event schedule. Any clinically significant abnormalities persisting at the end of treatment will be followed by the investigator until resolution or until a clinically stable endpoint is reached or until the end of the study.

Adverse Events

All adverse events will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. Adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to ibrutinib/placebo. Progressive disease of lymphoma should not be reported as an adverse event, but instead, the clinical symptom(s) that is associated with disease progression should be reported. All events that meet the definition of a serious adverse event will be reported as serious adverse events.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. 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. Adverse events will be graded according to the NCI-CTCAE, Version 4.03.

All deaths, treatment discontinuations, and serious adverse events will be reviewed by the sponsor's responsible physician, who will be blinded to treatment group. Review will be performed on an ongoing basis to identify potential safety concerns for further review by the DMC.

Adverse Events of Interest

Major hemorrhage has been identified as an adverse event of special interest and will require enhanced reporting and data collection (See Section 12.3.3 for details).

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.

Blood samples to assess the safety of study drug 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 first dose of study drug. 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 study drug (dose change, 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 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 the Time and Events Schedule:

- Hematology Panel

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

- Coagulation Studies

  -aPTT (activated partial thromboplastin time)
  -INR/PT (international normalized ratio/prothrombin time)

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -total bilirubin
  -albumin
  -AST
  -ALT
  -lactate dehydrogenase
  -alkaline phosphatase

- 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 negative for Hepatitis surface antigen but positive for Hepatitis B core antibody do not require PCR testing and may be included in the study with prophylaxis. All other subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization, and may be included in the study following consultation with an infectious disease specialist. 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.

Carriers of Hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for several months following rituximab treatment.

- Pregnancy test (serum β-hCG or urine): for women of childbearing potential only
- $Beta_2$- microglobulin and serum immunoglobulin levels (IgG, IgM, IgA)

Vital Signs

Temperature, heart rate, and blood pressure will be recorded at Screening and at the timepoints shown in the Time and Events Schedule. 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 chemotherapy 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 Time and Events Schedule.

Physical Examination

The Screening physical examination will include, at a minimum, the general appearance of the subject, height and weight, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. During the Treatment Phase, limited symptom-directed physical examination and weight assessment is required. Review of symptoms 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. An assessment of lymphoma B-symptoms (fever, night sweats and weight loss), change in status of lymph nodes, liver and spleen should also be conducted.

Echocardiogram or Multiple Uptake Gated Acquisition (MUGA) scans

An echocardiogram or multiple uptake gated acquisition (MUGA) scan is mandatory at screening for all subjects. Subjects who will receive R-CHOP must have left ventricular ejection fraction within institutional normal limits at screening. Echocardiogram may be performed thereafter, at any time during the study, as clinically indicated.

Electrocardiograms

Electrocardiogram will be performed for all subjects during Screening. Abnormalities noted at screening should be included in the medical history. Electrocardiograms may be repeated at any time during the study, as clinically indicated, particularly in subjects with arrhythmic symptoms (palpitations, lightheadedness, or new onset dyspnea).

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, or has not been lost to follow up or withdrawn consent before the end of the study.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment (ibrutinib or placebo) should be discontinued if:

- the investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- the subject becomes pregnant
- the subject experiences overt disease progression or relapse; however, if the subject has radiographic progression without clinical progression and alternate therapy is not initiated, study treatment may continue at the discretion of the investigator
- unacceptable toxicity

- the subject refuses further treatment with the study drug
- administration of study drug is interrupted for more than 4 weeks due to drug-related toxicities
- a serious protocol violation has occurred that may compromise subject safety, as determined by the principal investigator or the sponsor

If a subject discontinues background chemotherapy, they will continue to receive study drug (ibrutinib or placebo) until one of the reasons for discontinuation of study drug given above is met.

If a subject discontinues study drug only, they will continue to receive background chemotherapy until completion of 6 cycles unless disease progression or unacceptable toxicity is encountered. End-of-Treatment and posttreatment assessments should be obtained and scheduled disease assessments should be continued until they complete the study.

If a subject discontinues study treatment (both study drug and background chemotherapy), EOT and posttreatment assessments should be obtained and scheduled assessments should be continued until they complete the study.

10.3. Withdrawal From the Study

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

- lost to follow-up
- withdrawal of consent
- the sponsor discontinues the study

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. If a subject withdraws from the study before the end of the treatment phase, EOT assessments should be obtained.

11. STATISTICAL METHODS

Statistical analysis will be performed 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:

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.

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. Details of the exact criteria defining this population will be specified in the statistical analysis plan.

Biomarker population: All randomized subjects with biomarker data collected.

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/R-CHOP + placebo) is 20 months from randomization (Fowler 2011; Friedberg 2011), a target hazard ratio of 0.7 corresponds to an 8.6 months increase in median PFS for the treatment arm (BR/R-CHOP + ibrutinib) relative to the control (ie, 20 months versus 28.6 months, respectively)

c. minimum 80% power

d. 2-sided overall significance level of 0.05

e. one interim analysis for efficacy at 60% of the planned total PFS events

Using the above assumptions and based on a uniform accrual rate of approximately 26 subjects per month, the study will enroll approximately 400 subjects (about 200 subjects to each arm) to observe 252 events in approximately 43 months from the first subject randomized. The length of time required to observe the targeted number of events would be longer if subjects were to withdraw from the study before events were observed.

The data cutoffs based on the interim and primary analysis (ie, final analysis of the primary endopoint PFS) will be when about 151 and 252 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 20 months to 28.6 months), the study has at least 80% power assuming a statistical significance level of 5% (2-sided).

11.3. Efficacy Analyses

Descriptive statistics and subject listings 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. Specific details will be provided in the Statistical Analysis Plan.

Comparisons between the 2 treatment arms will be performed as follows: for the continuous variables representing change from baseline to a particular postbaseline timepoint, analysis of variance will be used. For discrete variables, Cochran-Mantel-Haenszel Chi-square test will be used. For time-to-event variables, stratified log-rank test and stratified Cox proportion hazard model will be used unless if specified otherwise. All tests will be conducted at a 2-sided alpha level of 0.05 and 95% CI will be provided, unless stated otherwise.

11.3.1. Primary Endpoint

The primary efficacy analysis will be based on the PFS and will be performed using the ITT population, which is defined as all randomized subjects. The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The stratified log-rank test will be used to compare survival curves of PFS between the 2 treatment groups. The median PFS will be provided for each treatment group and the hazard ratio for (BR or R-CHOP) + ibrutinib relative to (BR or R-CHOP) + placebo and its associated 95% CI will be calculated based on the Cox proportional hazards model stratified by the following stratification factors:

- background treatment (either BR or R-CHOP),
- iNHL histology (FL or MZL),
- refractory or relapsed disease (refractory defined as failing to achieve PR or better after the most recent treatment),
- prior lines of therapy (1 or >1 line of therapy. Separate lines of therapy are defined as different regimens that are separated by disease progression, refractory disease, or relapsed disease).

Hypothesis testing for the interaction between background therapy and treatment will be performed. If a significant interaction is observed, then the statistical inference for the treatment benefit will be made for each background therapy separately.

Subgroup analysis will be provided. 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. Detailed PFS censoring rules and other sensitivity analyses will be specified in the Statistical Analysis Plan.

11.3.2. Secondary Endpoints

For the secondary efficacy endpoints, OS will be compared using the stratified log-rank test. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. The hazard ratio for (BR or R-CHOP) + ibrutinib relative to (BR or R-CHOP) + placebo and its associated 95% CI will be calculated based on the stratified Cox proportional hazards model. The CR rate and ORR will be summarized and comparison of the rates between the 2 treatment groups will be performed using the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors. The distribution of duration of response will be estimated using the Kaplan-Meier product limit method for those subjects with CR or PR. Multiplicity adjustments will be made for the

hypothesis testing of secondary endpoints. Details will be specified in the statistical analysis plan. See Section 11.3.4 for details on the secondary endpoint FACT-Lym PRO analyses.

11.3.3. Exploratory Efficacy Endpoints

Time-to-next treatment is measured from the date of randomization to the start date of any anti-lymphoma treatment subsequent to the study treatment. Subjects without subsequent treatment will be censored at the date of the last site visit. The distribution of time-to-next treatment will be estimated using the Kaplan-Meier product limit method. See Section 11.3.4 for details on the exploratory endpoint EQ-5D-5L PRO analyses.

11.3.4. Patient-Reported Outcomes

Time to worsening (TTW) on the Lym subscale of the FACT-Lym is defined from the date of randomization to the start date of the worsening of patient symptoms. Worsening is defined by a 5-point decrease from baseline in patient symptoms. The analysis of TTW will be analyzed using log-rank test. The distribution of TTW will be estimated using the Kaplan-Meier product limit method.

Descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum) of FACT-Lym subscale and EQ-5D-5L scores will be calculated for baseline and postbaseline assessments, as well as change from baseline to postbaseline assessments. Other exploratory analyses may be performed as appropriate.

11.4. Pharmacokinetic Analyses

The plasma concentration data for ibrutinib and, if possible and judged relevant, PCI-45227 at each timepoint will be summarized using descriptive statistics. 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 per treatment group. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic parameters (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.

11.5. Biomarker Analyses

The MRD negative rate will be evaluated in FL subjects within and between treatment arms of this study. Biomarkers identified in other studies of ibrutinib will be explored in samples collected for MRD assessment. 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). Results may be presented in a separate report.

11.6. Safety Analyses

All safety analyses will be based on the safety population and will be performed by the treatment actually received. 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 current Medical Dictionary for Regulatory Activities. 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. Treatment-emergent adverse events are adverse events that occur after the first dose of study drug, and within 30 days following the last dose of study drug; any adverse event that is considered study drug-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI-CTCAE, Version 4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a serious adverse event.

Clinical Laboratory Tests

Hematology and serum chemistry laboratory data up to 30 days after last dose or EOT visit date, whichever is later, will be reported in International System of Units. 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 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. Shift tables from baseline to worst value on study (from treatment

start to 30 days after the last dose or the End-of-Treatment Visit date, whichever is later) will also be provided. The worst toxicity grade during the study will be tabulated.

Vital Signs

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

Electrocardiogram data at baseline will be summarized.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.7. Interim Analysis

An interim analysis using classical O'Brien & Fleming boundary for efficacy will be conducted after observing approximately 60% (151) PFS events (PD or death) (O'Brien 1979). The stopping boundaries will be implemented by Lan-Demets spending function using East® software v5.3 to control the 2-sided Type I error of 0.05 for the comparison of the PFS endpoint. The 2-sided cumulative alpha spent will be 0.0076 at the interim and 0.05 at the final analysis. Assuming the enrollment rate is 26 subjects per month, the interim analysis will take place approximately 25 months after the first subject has been randomized. The independent DMC may make recommendations regarding study continuation if the pre-specified boundary is crossed for efficacy. The roles and responsibilities of the DMC will be detailed in the DMC Charter.

11.8. 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 unblinded data on an ongoing basis to ensure the safety of the subjects enrolled in this study and evaluate efficacy.

In addition to the planned interim analysis for efficacy, 3 safety review meetings are planned that will occur approximately 2 months after 80 subjects have been randomized (20% of expected enrollment), 2 months after 200 subjects have been randomized, and 2 months after all 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 DMC chair may request additional safety interim analyses and more frequent monitoring. The plan for monitoring subject safety and evaluating efficacy, and the roles and responsibilities of the DMC, will be detailed in the 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 can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

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

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

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An 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 BR and R-CHOP, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable package insert.

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 drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- overdose of a sponsor study drug
- suspected abuse/misuse of a sponsor study drug
- inadvertent or accidental exposure to a sponsor study drug
- medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

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 adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of ibrutinib or the start of subsequent systemic anticancer therapy if earlier. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 for the entire follow-up period including post-progression follow-up for OS.

Progressive disease (for which there are protocol-specific assessments), should NOT be reported as an adverse event, but instead symptoms/clinical signs of unexpected disease progression are to 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 study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. 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.

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

- study number
- statement, in the local language(s), that the subject is participating in a clinical study
- investigator's name and 24-hour contact telephone number
- local sponsor's name and 24-hour contact telephone number (for medical staff only)
- site number
- subject number
- 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 can be attributed to agents other than the study drug or to factors unrelated to study conduct
- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- 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, scans, sampling for laboratory tests, bone marrow sampling) or protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.3. Adverse Events of Special Interest

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

12.3.3.1. Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic adverse events 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. 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 INFORMATION

14.1. Physical Description of Study Drugs

Study drugs (ibrutinib and placebo) are provided as a hard gelatin capsules containing 140 mg of PCI-32765 or placebo. All formulation excipients are compendia and are commonly used in oral formulations. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Study drugs are packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All bottles will utilize child resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Study drug supplies will contain a study-specific label with a unique identification number.

14.4. Preparation, Handling, and Storage

The recommended storage condition for study drug capsules is controlled room temperature (15ºC to 25ºC). 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 pharmacy manual/study site investigational product manual for additional guidance on study drug handling and storage conditions.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug 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 drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the

same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Protocol
- Investigator Brochure
- Pharmacy manual/study site investigational product manual]
- Laboratory manual and laboratory supplies
- PRO questionnaires
- Revised Response Criteria for Malignant Lymphoma (Cheson 2007)
- IVRS/IWRS Manual
- Electronic data capture (eDC) Manual and CRF completion guidelines
- Sample ICF
- Subject information materials

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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

The total blood volume to be collected is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the timeframe 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

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study. 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 can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects 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 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. 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.

16.2.6. 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 FL and/or MZL, to understand differential drug responders, and to develop tests/assays related to ibrutinib and FL and/or MZL. 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 their consent for their samples to be stored for research (refer to Section 10.3).

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 study drug to the study site:

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification

and 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; study drug administration information; and date of study completion and reason for early discontinuation of study drug 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).

Subject- and investigator-completed scales and assessments designated by the sponsor will be recorded directly into an electronic device and will be considered source data.

17.5. Case Report Form Completion

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

Electronic Data Capture (eDC) 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 verify 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 can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can 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, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for 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/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the 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 assessment 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 assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection 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 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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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 biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the

investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 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: Sample Questionnaire FACT-Lym

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 2: 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

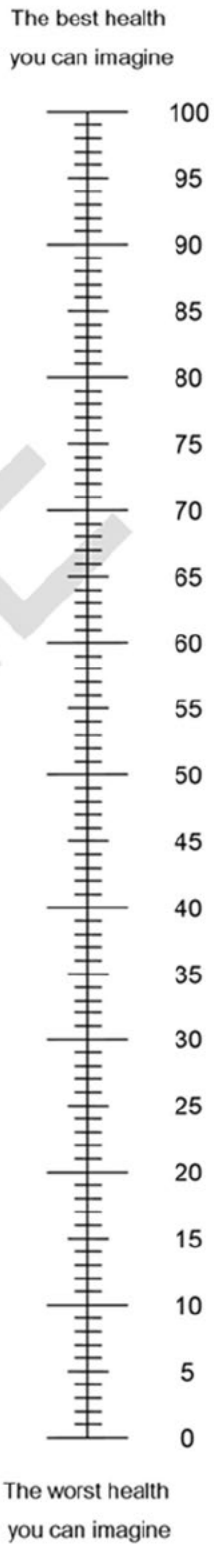
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 3: Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$C_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{(\text{Serum creatinine mg/dL}) \times 72}$$

Note:

- Multiply by 0.85 for women
- Use with caution in cirrhosis and muscle wasting
- To convert μmol (micromoles)/L of creatinine to mg/dL, divide by 88.4.

Cockroft D, Gault MK. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Attachment 4: Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx and http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables. 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

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib)
Clinical Protocol PCI-32765FLR3001 Amendment INT-3

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 102
Status: Approved, Date: 29 August 2022