Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma

Protocol PCI-32765DBL3001; Phase 3

Amendment INT-3

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 1, 2, and 3 clinical studies.

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

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	1 May 2013
Amendment INT-1	21 Dec 2013
Amendment INT-2	5 Aug 2015
Amendment INT-3	16 Oct 2017

Amendments are listed beginning with the most recent amendment.

Amendment INT-3 (16 Oct 2017)

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

The overall reason for the amendment: To omit the interim analysis due to a lower than expected event-free survival (EFS) event rate observed. To change retrospective analysis of the activated B cell-like (ABC) diffuse large B-cell lymphoma (DLBCL) population by gene expression profiling (GEP) from a secondary objective to a co-primary objective (ie, in addition to the already pre-specified non-germinal center B cell-like [non-GCB] DLBCL population by immunohistochemistry [IHC]). The hypothesis and primary endpoint analysis were updated to include the ABC by GEP population and the statistical method was clarified.

Applicable Section(s)	Description of Change(s)
Rationale: The sponsor is omitting the interim analysis due to a lower than expected EFS rate and the short time between when sufficient EFS events are projected to be reached for the interim analysis (ie, approximately 270 EFS events) and when the final analysis will be performed (fixed date; clinical cutoff is 30 months after the 800th subject is randomized).	
9.1.5 Clinical Cutoff; 11.3 Sample Size Determination; 11.9 Interim Analysis	Clarified language since the interim analysis is being omitted due to the low event rate and short time between the interim analysis (event-driven) and final analysis (fixed date).
Rationale: Since the initiation of this study**,** GEP is now a more readily available assay platform used for DLBCL subtyping in standard practice using commonly available formalin-fixed paraffin-embedded tissue (FFPE). Therefore, available tumor samples will be retrospectively analyzed to identify the ABC DLBCL population using GEP and the ABC subtype of DLBCL by GEP is being included as part of the primary endpoint analysis.	
Synopsis (Primary Objective; Secondary Objectives); 2.1 Objectives (Primary Objectives; Secondary Objectives)	Updated to add evaluation of the treatment benefit of subjects with the ABC subtype of DLBCL by GEP as a primary objective and remove as a secondary objective.
Synopsis (Hypothesis); 2.2 Hypothesis	Updated the study hypothesis to also include evaluation of the treatment benefit of subjects with the ABC subtype of DLBCL identified by GEP.
Synopsis (Overview of Study Design); 1.4 Overall Rationale for the Study; 3.1 Overview of Study Design	Clarified that available tumor samples will be retrospectively analyzed to identify the ABC DLBCL population using GEP now that this assay platform is more readily available; included supportive background rationale.

9.4.1 Companion Diagnostic	Clarified that [redacted] (a diagnostic GEP manufacturer) is developing a GEP assay for identification of the ABC DLBCL subtype (in addition to the already pre-specified IHC assay) that will be retrospectively determined using available clinical study FFPE tissue specimens.
11.1 Analysis Populations	Clarified definition for the ITT population and added the ABC population description.
11.4 Efficacy Analyses	Clarified that the primary endpoint analysis will use the Song and Chi method.
11.3.1 Multiplicity Adjustment for the ABC Subtype; References	Section added to describe revised statistical method (Song and Chi) to be used to analyze the ABC by GEP DLBCL population. References added.
Synopsis (Statistical Methods); 11.4.1 Primary Endpoint	Primary endpoint analysis was clarified for ABC by GEP population.
Synopsis (Secondary Objectives, Statistical Methods); 2.1; Objectives; 11.4.2 Secondary Endpoints; 9.2.3 Endpoints	Updated the hierarchal order of the secondary efficacy endpoints (analysis of CR rate before overall survival).
Rationale: To clarify data to be collected after the primary endpoint analysis.	
Synopsis (Efficacy Evaluations); Table 1 (Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis Table 3 (Time and Events Schedule – After the Clinical Cutoff for the Primary Endpoint Analysis); 3.1 Overview of Study Design; 9.1.4 Posttreatment Follow-up Phase 9.2.1 Evaluations; 9.2.1.1 CT/MRI/PET Scans; 9.2.1.5 Patient-Reported Outcomes	Renamed and clarified heading in Table 1 to specify assessments to be performed up to clinical cutoff for primary endpoint analysis; Added Table 3 to clarify data to be collected after the primary endpoint analysis. Radiological disease evaluations are not required after the clinical cutoff for the primary endpoint analysis and may be performed as clinically indicated (at the discretion of the investigator) per local standard of care
Rationale: Clarification to end of study definition was provided.	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 9.1.5 Clinical Cutoff	Clarified definition of end of study: ie, when 50% of the randomized subjects have died **or 5 years after the last subject is randomized** or the sponsor terminates the study, whichever occurs first.
Rationale: Minor errors were corrected.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
References	Updated reference list per revised text.
9.1.4 Posttreatment Follow-up Phase; 9.2.1.1 CT/MRI/PET Scans	Removed reference to specific assessment timepoints to streamline document (retain details in Time and Events Schedule)
9.5 Safety Evaluations	Correction made to clarify that adverse events reported after 30 days following the last dose of study treatment should be reported if considered related to “study treatment” (not ibrutinib/placebo)

Rationale: Updates were made to align with current protocol template as appropriate.	
Title page	Updated sponsorship statement.
17.3 Subject Identification, Enrollment, and Screening Logs	Clarified that date of birth for subject identification (eg, in reports and communications) will only be used as allowed by local regulations.
17.11 Publications	Clarified timing for publication of study results. Clarified guidelines and criteria used for named authors in publications.

Amendment INT-2 (5 Aug 2015)

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

The overall reason for the amendment: To clarify protocol recommendations for monitoring of patient subgroups who are considered, based on emerging literature, at increased risk of hepatitis B virus reactivation due to R-CHOP + ibrutinib/placebo therapy. Additionally, the protocol was updated with new safety-related information for consistency with the ibrutinib Investigator's Brochure.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects who are at increased risk of potentially fatal hepatitis B virus reactivation as a consequence of R-CHOP + ibrutinib/placebo anti-B-cell drug treatment should be monitored to guide antiviral therapy.	
Time and Events Schedule (note 'n'); 8.1.2. Medications Permitted During Treatment; 9.5. Safety Evaluations	• Clarified the requirement for hepatitis B DNA by PCR testing at screening, and confirmation of a negative finding for this test, to include subjects testing positive for hepatitis B surface antigen (in addition to those testing positive for hepatitis B core antibody). • Clarified prophylactic antiviral therapy in subjects who are hepatitis B surface antigen positive/hepatitis B DNA by PCR negative, according to local guidelines. • Added prophylactic antiviral therapy or monitoring in subjects who are hepatitis B core antibody positive/hepatitis B DNA by PCR negative, according to local guidelines. • Clarified monitoring of hepatitis B carriers during and after anti-B-cell treatment, according to local guidelines.
Rationale: To clarify the follow-up period for the interim analysis, as the language is inaccurate in stating that this is estimated to occur approximately 6 months after the last subject is enrolled. The interim analysis is event-driven. For the second clinical cutoff for the final EFS analysis, we are clarifying that the cutoff will occur 30 months after the '800th' subject is randomized instead of 'last subject' randomized.	
Synopsis; 9.1.5. Clinical Cutoffs; 11.3. Sample Size Determination; 11.9 Interim Analysis	With a study follow-up period of 30 months after the 800th subject is randomized, it is anticipated that approximately 419 EFS events will be observed and the study will have at least 90% power to show the statistical significance at the overall alpha level of 0.025 (1 sided). The interim analysis will occur when approximately 270 EFS events have been observed. The clinical cutoff for the final EFS analysis is 30 months after the 800th subject randomized.
Rationale: To update the Sponsorship statement.	
Title page	In the Sponsorship statement, replaced "Janssen R&D Ireland" with "Janssen Sciences Ireland UC".
Rationale: To update the name of the co-development company for ibrutinib from Pharmacyclics, Inc to Pharmacyclics LLC.	

Applicable Section(s)	Description of Change(s)
Synopsis; 1. Introduction	Pharmacyclics, Inc has been replaced by Pharmacyclics LLC.
Rationale: A correction has been made to the criteria used to determine complete response.	
9.2.2.3. Response Categories	The length of the short axis of previously involved nodes before treatment has been corrected from 1.1 cm to 1.0 cm.
Rationale: Language describing health authority approvals for ibrutinib has been made more general, to avoid the need for future updates to this text.	
Synopsis; 1. Introduction	Rather than describe the current U.S. FDA approvals for ibrutinib, the initial approval (adult patients with mantle cell lymphoma who have received at least 1 prior therapy) is noted instead.
Rationale: The definition for the adverse event of special interest of major hemorrhage has been clarified, and intracranial hemorrhage is subsumed within the new definition for major hemorrhage.	
Synopsis Safety Evaluations; 9.5. Safety Evaluations; 12.3.3.1. Major Hemorrhage	Intracranial hemorrhage is no longer mentioned separately from major hemorrhage; rather, it is subsumed within the new definition for major hemorrhage.
Rationale: Clarifications have been made to the description of the investigational product, for consistency with the ibrutinib Investigator's Brochure.	
1.2. Investigational Product Name and Description	Ibrutinib is described as a white to off-white solid, provided in an oral capsule formulation.
Rationale: Results from a recent hepatic impairment study performed in non-cancer 526 subjects administered a single dose of 140 mg ibrutinib are available and were added to the background section of the protocol.	
1.3.2. Clinical Pharmacokinetic Data (Summary of Human Pharmacokinetics)	In a hepatic impairment study, data showed an increase in ibrutinib exposure following single dose administration in subjects with mild, moderate, and severe hepatic impairment compared to subjects with normal liver function.
Rationale: Clinical safety information for ibrutinib monotherapy studies has been updated for consistency with both the ibrutinib Investigator's Brochure and other protocols within the ibrutinib clinical development program.	
1.3.4. Clinical Safety of Ibrutinib; 1.3.4.1.1. Hematological Adverse Events; 1.3.4.1.2. Non-Hematological Adverse Events	Clinical safety information for ibrutinib monotherapy studies has been updated and reorganized 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; rash and tumor lysis syndrome).
Rationale: The timing of required laboratory assessments at screening has been further clarified to minimize confusion.	
4.1. Inclusion Criteria (Criteria 8 and 9)	Inclusion criteria 8 (hematology values) and 9 (biochemical values) specify limits that must be met prior to randomization and at baseline. The qualifier 'within 14 days' has been removed from both criteria.
Rationale: This section has been revised to clarify that a short ibrutinib hold (up to 3 days) should be considered for intrathecal CNS prophylaxis based upon the subject's clinical situation, including assessment of underlying lymphoma.	
4.3. Prohibitions and Restrictions	From bullet #2 within this section, the word 'minor' has been deleted within 'minor procedures'. Also within bullet #2, for the list of procedures requiring ibrutinib to be held, 'intrathecal CNS prophylaxis' has been added.

Applicable Section(s)	Description of Change(s)
Rationale: Dose modification for hematologic toxicities related to cyclophosphamide and doxorubicin, and maximum allowed dose of prednisone administered for reason other than cancer, have been clarified based on investigator feedback.	
6.2.2. Cyclophosphamide; 6.2.3. Doxorubicin;	Within Sections 6.2.2 and 6.2.3, dose adjustments for hematologic toxicities are now recommended rather than mandated.
Rationale: To clarify that chronic use of corticosteroids (ie, prednisone ≤20 mg/day or its equivalent) is allowed for other non-cancer related medical reasons during the treatment phase.	
8.2. Prohibited Medications	Chronic use of systemic corticosteroids above that given for R-CHOP chemotherapy are prohibited. However, prednisone ≤20 mg/day or its equivalent is allowed for the treatment of adrenal insufficiency or other medical reason that is not cancer related.
Rationale: Guidance for certain categories of concomitant medications has been updated for consistency with the current ibrutinib Investigator's Brochure.	
8.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib; 8.2.4. Concomitant Use of Ibrutinib/Placebo and Antiplatelet Agents and Anticoagulants	Guidance for administration of ibrutinib with narrow therapeutic range P-gp substrates has been added to Section 8.2.2. Guidance for administration of ibrutinib/placebo in subjects requiring therapeutic anticoagulation therapy has been clarified within Section 8.2.4.
Rationale: To avoid enrolling subjects in whom R-CHOP dose reductions are inevitable.	
9.1.2. Pretreatment (Screening) Phase	Statement has been added requiring investigators to confirm that subjects who are ≥80 years old are eligible to receive R-CHOP according to the protocol, without preplanned dose reductions.
Rationale: Clarified the minimum criteria that have to be present in the local pathology report for DLBCL diagnosis.	
9.1.2. Pretreatment (Screening) Phase	Requirements for the local pathology report, allowing verification of the DLBCL diagnosis, have been clarified.
Rationale: Safety data from a Phase 3, randomized comparator-controlled (ibrutinib versus ofatumumab) study of ibrutinib monotherapy in subjects with CLL/SLL (ibrutinib: 195 subjects; ofatumumab: 191 subjects) 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.	
9.5. Safety Evaluations (Physical Examination)	Physical examinations conducted during the Active Treatment Phase will include monitoring for ocular symptoms.
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	Text has been expanded to show that in addition to electrocardiograms performed for all subjects during Screening, electrocardiograms may be repeated at any time during the study, as clinically indicated, especially in subjects with symptoms of arrhythmia.
Rationale: For consistency with risk-based monitoring text in current protocol template.	

Applicable Section(s)	Description of Change(s)
17.8. Monitoring	Three new paragraphs have been added to this section, addressing: • Sponsor will use a combination of monitoring techniques. • Remote contacts. • Central monitoring/central review. Additionally, text has been added stating that only a sample of data may be reviewed.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (21 Dec 2013)

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

The overall reason for the amendment: To remove the biopsy/tissue requirement for confirmation of DLBCL diagnosis; update the protocol with new safety-related information and instructions; further clarify study treatment dosing instructions; revise operational aspects of the study; and perform minor modifications and formatting changes.

Applicable Section(s)	Description of Change(s)
Rationale: Tissue was being collected to both confirm DLBCL diagnosis and to determine the molecular subtype (non GCB vs. GCB subtype). Collection of tissue for confirmation of DLBCL diagnosis is no longer required (pathology report is sufficient); this will minimize burden to study subjects and clinical sites. The potential benefit of confirming the DLBCL diagnosis with the additional biopsy/tissue sample is considered to be small and removing central pathology confirmation of DLBCL imparts no risk to the study's objectives. Alternatively, the sponsor will collect local pathology reports to determine the incidence of misdiagnosis and sensitivity analyses to the primary analysis will be considered if substantial misdiagnosis is suspected.	
Synopsis; Time and Events Schedule; 3.1 Overview of Study Design; 4.1 Inclusion Criteria (criterion 3); 9.1.2 Pretreatment (Screening) Phase; Figure 1	Wording revised to remove requirement for tissue collection at screening for confirmation of DLBCL diagnosis. Figure 1 (study schema) updated to reflect this.
Rationale: Clarification that uric acid is part of the chemistry panel on Day 1 of each cycle to allow for monitoring of tumor lysis syndrome. Also clarified that biochemistry tests may be repeated as clinically indicated.	
Time and Events Schedule	On Day 1 of each cycle starting with Cycle 2: sodium, potassium, creatinine, total bilirubin, uric acid, and LDH. Magnesium on Day 1 of Cycles 1 and 2. Biochemistry tests may be repeated as clinically indicated.
Rationale: Clarification to the mechanism of action of ibrutinib.	
Synopsis; 1 Introduction	Based on current information, the description of the mechanism of action of ibrutinib as a potent, orally-administered, covalently-binding small molecule Bruton's tyrosine kinase (BTK) inhibitor has been updated in the protocol.
Rationale: On November 13, 2013 the FDA approved ibrutinib for the treatment of patients with MCL who have received at least 1 prior therapy. Therefore, the statement indicating that ibrutinib has not been approved for marketing in any country has been deleted and a statement on the current US approval in MCL has been added.	
Synopsis; 1 Introduction; 1.2 Investigational Product Name and Description	Added: Ibrutinib (IMBRUVICA™) is approved by the U.S. Food and Drug Administration for the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified that the components of the R-CHOP regimen can be administered over 2 days.	
Table 2, Dose and Administration Schedule for R-CHOP	The components of the R-CHOP regimen can be given over 2 days.
Rationale: Updated nonclinical statement on growth inhibition for specificity on DLBCL cell lines and to align with current Investigator's Brochure.	
1.3.1 Nonclinical Data	Ibrutinib inhibited the proliferation of cell lines derived from DLBCL patients with a median effective concentration of 1 or 2 nM.
Rationale: The average increase (ie, 26-fold) in ibrutinib exposure when administered in combination with ketoconazole was provided in the protocol. The protocol has been updated with the actual increase for the C_{max} and $AUC_{0\text{-last}}$. A cross-reference to Section 8.2.1 was added for additional guidance on concomitant use of ibrutinib/placebo with CYP3A inhibitors or inducers. In addition, updated text within Pharmacokinetic and Pharmacodynamic subsection of Section 1.3.2 to align with the current Investigator's Brochure.	
1.3.2 Clinical Pharmacokinetic Data; 8.2.1 Concomitant Use of Ibrutinib/Placebo and CYP3A Inhibitors/Inducers	Ketoconazole, a strong CYP3A inhibitor, increased ibrutinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration [$AUC_{0\text{-last}}$]) by 29- and 24-fold, respectively. Bruton's tyrosine kinase remained fully occupied by ibrutinib (≥90% occupancy) for at least 24 hours in all subjects in Cohorts 2 through 5 (2.5 to 12.5 mg/kg/day) and for the 560 mg continuous dosing cohorts.
Rationale: Updated available efficacy data in subjects with DLBCL from Study PCI-32765DBL1002.	
1.3.3.4 Study PCI-32765DBL1002; Table 4	Response data suggest activity with this regimen, with 18/18 (100%) evaluable subjects with DLBCL treated at a dose of 560 mg ibrutinib + R-CHOP achieving a response (14 CRs and 4 PRs).
Rationale: Safety data, since the time the original protocol was finalized, have been updated. These data include information from the 2013 Investigator's Brochure, PCYC-04753 CSR, and preliminary safety results for Study PCI-32765DBL1002 (data cutoff of 08 July 2013).	
1.3.4 Clinical Safety of Ibrutinib; 1.3.2 Clinical Pharmacokinetic Data	At the time of the original protocol (1 May 2013), safety data for 312 subjects were available, which was consistent with the Investigator's Brochure at the time of protocol finalization. Safety data as of 06 Apr 2013 for the 506 subjects treated with ibrutinib monotherapy and 130 subjects treated with ibrutinib in combination with chemotherapy have been added. Data regarding hemorrhagic adverse events occurring in ibrutinib clinical studies have been updated. Preliminary safety data for Study PCI-32765DBL1002 was updated (clinical cutoff: 08 July 2013).
Rationale: Additional new safety information (other malignancies, rashes, and infection) based on studies conducted with ibrutinib has been added. Other malignancies occurring in subjects treated in this study will be reported and collected on the CRF. A description of other malignancies observed in subjects treated with ibrutinib is also provided.	

Applicable Section(s)	Description of Change(s)
Synopsis (Safety Evaluations); 1.3.4.4 Other Malignancies; 1.3.4.5 Rash; 1.3.4.6 Infection; 9.1.4 Posttreatment Follow-up Phase; 12.3.4 Other Malignancies	In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies, and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS. In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥ Grade 3; 25.2%) and CLL/SLL (≥ Grade 3; 35.3%). Some of these infections have been associated with hospitalization and death. Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.
Rationale: All imaging evaluations and radiology reports must be readily available if requested by the sponsor; images must meet imaging requirements as specified in the radiology manual. Also clarified that a PET/CT may be submitted in lieu of a dedicated CT if it is of diagnostic quality.	
Synopsis; 3.1 Overview of Study Design; 9.2.1 Evaluations; 15 Study-Specific Materials	Radiological and PET scans performed prior to the database lock for the final analysis of EFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary. A separate CT scan is 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 if it is of diagnostic quality. The CT scanning must be done according to the imaging requirements provided in the radiology manual to ensure that an optimized examination is done.
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) as well as the timing if a dose is missed (ie, up to 6 hours after a meal). Furthermore, instructions for fasting prior to collection of pharmacokinetic samples have been deleted.	
6.1.2 Ibrutinib or Placebo Administration	Ibrutinib/placebo capsules should be swallowed whole and should not be opened, broken, or chewed. If a dose of study drug is missed it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.
9.3.1 Evaluations	Deleted: 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.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified throughout protocol that study treatment may continue if study drug (ibrutinib or placebo) is delayed, withheld, or discontinued.	
Synopsis; 6.2 Dose Modifications and Dose Delay; 10.2 Discontinuation of Study Treatment	Subjects who discontinue any component of R-CHOP without disease progression will continue study drug (placebo or ibrutinib) until 6 or 8 cycles are completed (as pre-specified by each site), disease progression, or unacceptable toxicity, whichever occurs first. If study drug is discontinued, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may continue. If R-CHOP is delayed, treatment with study drug should be continued during the delay phase. If the study drug (ibrutinib/placebo) is delayed or withheld, R-CHOP treatment may be continued if clinically indicated.
Rationale: Throughout the protocol references to 'study drug' - meaning ibrutinib or placebo - versus 'study treatment' - meaning ibrutinib or placebo plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone have been clarified. Examples or characterization of the changes are provided below.	
Synopsis; Time and Events Schedule; 1.3.5 Background Therapy; 3.1 Overview of Study Design; 6 Dosage and Administration; 7.1 Ibrutinib or Placebo Compliance; 8 Prestudy and Concomitant Therapy; 9.1.3 Active Treatment Phase; 9.3.1 Evaluations; 9.5 Safety Evaluations; 10.2 Discontinuation of Treatment; 11.8 Safety Analyses; 12.2 Special Reporting Situations; 12.3.1 All Adverse Events; 12.3.2 Serious Adverse Events; 14.3 Drug Accountability; 17.2.2 Required Prestudy Documentation; 17.4 Source Documentation	For the purposes of this study, 'study drug' refers to ibrutinib or placebo and 'study treatment' refers to ibrutinib/placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (or equivalent). The Active Treatment Phase will begin at randomization and will continue until discontinuation of all study treatment (ie, ibrutinib/placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) due to disease progression, initiation of subsequent antilymphoma therapy, unacceptable toxicity, withdrawn, or completion of study treatment. The timeframe for collection of data on concomitant medications and adverse events, and study assessment and procedures now reference study treatment instead of study drug, where applicable. An End-of-Treatment Visit will be scheduled within 30 days after the last dose of the last study treatment. The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. Section 1.3.5 heading title renamed from "Study Drugs Used as Background Therapy" to "Background Therapy" since "study drug" is defined as ibrutinib or placebo.
Rationale: Clarified pre-treatment steroid instructions.	
8.1.1.1 Pre-treatment Steroids	If pre-treatment steroids exceed 10 days or 100 mg/day, please consult the medical monitor for approval.
Rationale: Instructions for dose modification for cyclophosphamide and doxorubicin for hematological toxicities was updated to align with global treatment practices.	

Applicable Section(s)	Description of Change(s)
6.2.2 Cyclophosphamide	To start a cycle with cyclophosphamide, ANC must be ≥1,000/µL and platelets ≥75,000/µL. The cycle must be delayed up to 3 weeks (instead of 2 weeks as previously specified) until the above values are documented on Day 1 of the cycle. For ANC <500/µL and/or febrile neutropenia, initiation of G-CSF for all subsequent cycles is recommended. Dose reductions due to low platelet counts or ANCs are not required in subjects with thrombocytopenia or neutropenia due to bone marrow infiltration from DLBCL who entered the study with platelet counts <75,000/µL or neutrophil counts <1,000 cells/µL.
Rationale: Instructions for Grade 3 or greater neutropenia with infection or fever have been added and instructions for any Grade 3 or greater non-hematological toxicity. Specific instructions for nausea, vomiting, and diarrhea have been removed.	
6.2.6 Ibrutinib or Placebo	Dose modification instructions were added for Grade 3 or greater neutropenia with infection or fever and any Grade 3 or greater non-hematological toxicity.
Rationale: Throughout the protocol, references to CYP3A4/5 have been corrected to CYP3A. Examples are provided below.	
1.3.2 Clinical Pharmacokinetic Data; 4.1 Exclusion Criteria; 6.1.2 Ibrutinib or Placebo Administration; 6.2.6 Study Drug (Ibrutinib or Placebo); 8.1 Permitted Medications and Supportive Therapies; 8.2.1 Concomitant Use of Ibrutinib/ Placebo and CYP3A Inhibitors/Inducers; Attachment 5	Subjects should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to CYP3A inhibition. All concomitant medications for medical conditions other than DLBCL NHL are permitted other than those listed as CYP3A inhibitors, as clinically indicated. Ibrutinib is metabolized primarily by CYP3A.
Rationale: Guidance for the administration of CYP3A inhibitors during ibrutinib/placebo administration is provided.	
8.2.1 Concomitant Use of Ibrutinib/Placebo and CYP3A Inhibitors/Inducers; Attachment 5, References	Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. A new reference website for inhibitors and inducers of CYP450 enzymes has been added.
Rationale: Instructions for drugs that may have their plasma concentrations altered by ibrutinib were added.	
8.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib	New text has been added to discuss the effect of ibrutinib as a weak inducer of CYP450 isoenzymes and a mild inhibitor of P-gp.
Rationale: QT prolongation is not expected with ibrutinib; however, text regarding the precaution for concomitant use of ibrutinib and medications known to cause QT prolongation has been added to align with the current Investigator's Brochure.	
8.2.3 Concomitant Use of Ibrutinib/Placebo and QT Prolonging Agents	Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECG) and electrolytes should be considered and, if needed, the medical monitor may be contacted.

Applicable Section(s)	Description of Change(s)
Rationale: Instructions for concomitant use of ibrutinib and antiplatelet agents, anticoagulants, and supplements such as fish oil and vitamin E preparations have been updated.	
8.2.4 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 preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
Rationale: To date, the ocular adverse events observed in subjects with ibrutinib alone do not indicate the need of additional monitoring. Therefore, this is no longer a required assessment.	
Time and Events Schedule; 9.1.3 Active Treatment Phase; 9.5 Safety Evaluations; 12.3.3.2 Intracranial Hemorrhage	Deleted review of ocular changes for physical examinations. The following text has been deleted: The examination should also include inquiry of ocular symptoms and subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.
Rationale: For subjects without progressive disease after the clinical cutoff, efficacy assessments will continue to be collected. Previously, efficacy assessments were to be collected according to the schedule outlined in the protocol. This has been changed to comply with the standard of care at the site.	
9.2.1.1 CT/MRI/PET Scans	Follow up visits, including CT scans, will be completed every 16 weeks for the first 24 months, then every 24 weeks until PD, the clinical cutoff for the primary endpoint, or up to 5 years. After that, CT may be performed only as clinically indicated per standard of care.
Rationale: Clarified text regarding fluid aspiration for other sites of disease	
9.2.1.3 Fluid Aspiration of Other Sites of Disease	For sites of disease with fluid accumulation such as 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 before disease progression is diagnosed for a subject if the fluid accumulation is the only sign of disease progression.
Rationale: Increased window for hematology and clinical chemistry assessments for flexibility at the sites.	
Time and Events Schedule; 9.5 Safety Evaluations	For Cycle 1 Day 1 only, if Screening tests were performed within 5 days of first dose of study treatment, then clinical laboratory tests do not need to be repeated. For subsequent cycles, samples can be taken within 3 days prior to dosing, provided that results are available before study treatment is given.
Rationale: Added details regarding the companion diagnostic procedures for determination of the DLBCL subtype.	
9.4 Companion Diagnostic and Biomarkers	Added subsections 9.4.1 (Companion Diagnostic) and 9.4.2 (for Biomarkers). A companion diagnostic device will be developed in parallel to the clinical study for determination of DLBCL subtype. The DLBCL Classification IHC [redacted] assay used to identify non-GCB and GCB subtypes is based on the Hans algorithm (2004) and utilizes a standardized immunohistochemistry protocol. Subtyping will be accomplished by determination of the status of CD10, BCL6, and MUM 1. Standardized protocols will be implemented at 4 regional central laboratories to ensure consistency in testing between each laboratory.
Rationale: Additional information for the Screening Hepatitis B and C sample collection has been added.	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule; 9.5 Safety Evaluations	Screening for Hepatitis B and C will include the following evaluations: Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody. Subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Subjects who test positive for Hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for Hepatitis C after completion of the treatment for hepatitis.
Rationale: Clarification on post-Screening vital sign procedures provided for completeness and consistency with Time and Events Schedule.	
9.5 Safety Evaluations (Vital Signs)	Heart rate and blood pressure will also be collected on Day 1 of each cycle and at the End-of-Treatment Visit.
Rationale: Clarified the study hypothesis method used to determine sample size. In this study, the primary endpoint analysis measures a combination of improvement in the cure rate and improvement in the EFS interval among those patients who are not cured. A wide range of outcomes may result in a statistically significant difference between the groups.	
11.3 Sample Size	Added text and table to describe the possible clinical outcomes and corresponding probability that such outcomes will result in a statistically significant difference between the groups, based on a median EFS of 12 months for non-cured subjects.
Rationale: Timing of safety review meetings has been revised for consistency with the Statistical Analysis Plan.	
11.10 Data Monitoring Committee	At the interim analysis, the DMC may recommend stopping the study for efficacy, if the pre-specified stopping boundary is crossed. In addition to the planned interim analyses for efficacy, 4 safety review meetings are planned that will occur approximately 2 months (not 1 month, as previously stated) after 50, 250, 450, and 650 subjects have been randomized.
Rationale: The list of study-specific materials provided to the sites has been revised according to company operational standards. Some of these items may be provided via other processes. The names of 2 forms have been revised.	
15 Study-Specific Materials; 10.2 Discontinuation of Study Treatment; 9.2.2.1 Assessment of Disease Response and Progressive Disease	The following materials have been removed from the list: ibrutinib and placebo capsules; package inserts for rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and the NCI-CTCAE Version 4.03. Added Imaging Manual to the list. The Eligibility Notification form was revised to the Diagnosis and subtyping report form. The Progressive disease notification form was revised to Study Event form.
Rationale: Throughout the protocol, minor grammatical, formatting, or spelling changes were made where required, or clarifications, if needed. Examples are provided below.	
Synopsis (Safety Evaluations)	Clarified in the synopsis that enhanced reporting of adverse events of interest (intracranial hemorrhage, major hemorrhage) will be conducted and data on new malignancies will be collected.
5 Treatment Allocation and Blinding	Clarified that site personnel and the sponsor may be unblinded if treatment assignment information is needed to determine further actions to address an urgent safety concern.
9.1.3 Active Treatment Phase	Text on adverse event reporting deleted, as already included in Section 12, Adverse Event Reporting.
9.2.1.1 CT/MRI/PET Scans	Clarified timing of End-of-Treatment scans (ie, added: at least 3 weeks but preferably 6 to 8 weeks, after the last dose of R-CHOP) as stated in Time and Events Schedule.

Applicable Section(s)	Description of Change(s)
9.5 Safety Evaluations (Vital Signs)	Clarified that “abnormal” vital signs considered to be clinically relevant are to be documented as adverse events.
12.3.1 All Adverse Events	Periodic reviews of the protocol template are conducted to provide corrections and improvements. Instructions for the subject “wallet (study) card” were clarified.
16.2.3 Informed Consent	Clarified that the molecular subtyping informed consent form may be obtained separately from the full study informed consent form.
16.2.5 Long-Term Retention of Samples for Additional Future Research	Clarification was made to explain the meaning of ‘differential drug responders’. This was changed to ‘differences in response’ to drug to the following: Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib, to understand DLBCL, to understand differences in response to drug and to develop tests/assays related to ibrutinib and DLBCL.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is a first-in-class, potent, orally-administered, covalently-binding small molecule BTK inhibitor 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 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 and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used.

It is increasingly appreciated that the diagnostic category of diffuse large B-cell lymphoma (DLBCL) is heterogeneous in terms of morphology, genetics, and biologic behavior. Gene expression profiling (GEP) and immunohistochemistry (IHC) are 2 of the assay platforms currently being used for determining cell of origin. Gene expression profiling platforms assign specimens into 1 of 3 diagnostic categories: germinal center B cell-like subtype (GCB), activated B cell-like subtype (ABC), or unclassified. Immunohistochemistry divides the population into non-germinal center B cell-like subtype (non-GCB) and GCB. Current evidence suggests that patients diagnosed with the non-GCB subtype of DLBCL, as compared to the GCB subtype, have inferior outcomes when treated with conventional therapy. Identifying and treating the non-GCB subtype with improved therapeutics represents a significant unmet medical need. Recently, Phase 1 and 2 studies suggest that ibrutinib is less active in subjects with GCB DLBCL and more active in subjects with non-GCB or specifically the ABC subtype. Interestingly, data also suggest that ibrutinib shows superior activity among DLBCL patients who are still chemosensitive. Together, these findings suggest a potentially important role for ibrutinib as front-line treatment in the non-GCB and ABC subtypes. Early data from an ongoing Phase 1 combination study show that ibrutinib can be safely combined with R-CHOP. This study will evaluate if ibrutinib in combination with R-CHOP improves the outcome in newly diagnosed patients with the non-GCB subtype of DLBCL selected by IHC or newly diagnosed patients with ABC subtype of DLBCL identified by GEP or both populations.

OBJECTIVES AND HYPOTHESIS

Primary Objective

To evaluate if the addition of ibrutinib to R-CHOP prolongs event-free survival (EFS) compared with R-CHOP alone in subjects with newly diagnosed non-GCB subtype of DLBCL selected by IHC or newly diagnosed patients with ABC subtype of DLBCL identified by GEP or both populations.

Secondary Objectives

To compare ibrutinib in combination with R-CHOP versus R-CHOP alone with regard to progression-free survival (PFS), complete response (CR) rate, overall survival, patient-reported lymphoma symptoms and concerns, and safety. Additional secondary objectives are to characterize the pharmacokinetics of ibrutinib and explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information.

Exploratory Objectives

To evaluate patient-reported outcomes (PROs) related to well-being and general health status utilizing the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and EuroQol (EQ-5D-5L) questionnaires and to explore the relationship between relevant biomarkers with clinical outcomes and mechanism of resistance.

Hypothesis

Ibrutinib in combination with R-CHOP will prolong EFS compared with R-CHOP alone in subjects with newly diagnosed non-GCB DLBCL selected by IHC or in subjects with newly diagnosed ABC DLBCL identified by GEP or in both populations.

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 R-CHOP versus R-CHOP alone in subjects 18 years and older with newly diagnosed non-GCB DLBCL. Prior to randomization, subjects with DLBCL are required to submit local pathology reports to a central laboratory for verification of diagnosis. In addition, all subjects are required to submit tumor samples to the central laboratory for determination of subtype (GCB versus non-GCB) by central IHC. Only subjects with newly diagnosed non-GCB subtype of DLBCL, as determined by IHC at a central laboratory, will be enrolled. Approximately 800 eligible subjects will be stratified by Revised International Prognostic Index (R-IPI; 1-2 vs. 3-5), region (US/Western Europe vs. Rest of World), and number of pre-specified treatment cycles (6 vs. 8 cycles), then randomized in a 1:1 ratio to receive either placebo+R-CHOP (Treatment Arm A) or 560 mg ibrutinib+R-CHOP (Treatment Arm B). Prior to treatment, sites will pre-specify treatment of subjects with either 6 or 8 cycles. The study will include a Pretreatment (Screening) Phase prior to randomization, an Active Treatment Phase (includes visits at the start of each cycle and an End-of-Treatment Visit [should occur 30 days after the last dose of the last study treatment]), and a Posttreatment Follow-up Phase until death, loss to follow up, consent withdrawal, or study end. It is expected that there will be 27 months of accrual, and the study will end when 50% of the randomized subjects have died or 5 years after the last subject is randomized or the sponsor terminates the study, whichever occurs first. Available tumor samples will be retrospectively analyzed to identify the ABC DLBCL population using GEP.

SUBJECT POPULATION

The study population will include subjects 18 years of age and older with newly diagnosed DLBCL and histological confirmation of the non-GCB subtype (by sponsor approved central laboratory) and Stage II (not candidates for local X-ray therapy) to Stage IV disease (by Ann Arbor Classification). Subjects must also have at least 1 measurable site of disease; an R-IPI score of ≥1; and an Eastern Cooperative Oncology Group performance status grade of 0, 1, or 2.

DOSAGE AND ADMINISTRATION

All subjects will receive R-CHOP (rituximab 375 mg/m^2 intravenous [IV], cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV [maximum total 2 mg], and prednisone [or equivalent] 100 mg orally) as background therapy for 6 or 8 cycles per site preference (21 days per cycle). Sites may choose to administer 6 or 8 cycles of treatment based on local practice; once the number of cycles is pre-specified by the site, all subjects at individual sites are intended to receive the same number of treatment cycles (6 or 8; no individual subject adjustment permitted based on interim response). Subjects will be randomized in a 1:1 ratio to Treatment Arm A (placebo, 4 capsules orally once daily continuously + R-CHOP) or Treatment Arm B (ibrutinib 560 mg [4 x 140 mg capsules orally once daily continuously + R-CHOP]) for 6 or 8 cycles, depending on the number of cycles pre-specified by each site. Study treatment administration begins on Cycle 1 Day 1 (within 72 hours of randomization) and ends on Day 21 of the last cycle, unless the subject experiences unacceptable toxicity or disease progression.

Subjects who discontinue any component of R-CHOP without disease progression will continue study drug (placebo or ibrutinib) until 6 or 8 cycles are completed (as pre-specified by each site), disease progression, or unacceptable toxicity, whichever occurs first. If study drug is discontinued, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may continue. Study drug (ibrutinib or placebo) should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity until recovery to Grade ≤1 or baseline. Dose reductions are permitted for recurring adverse events (ie, reduce to 420 mg on second occurrence, 280 mg on third occurrence, then discontinue on fourth occurrence of the same adverse event). Dose

escalation of study drug is not allowed. Dose modifications for R-CHOP should be done in accordance with the respective product labels, unless stated otherwise in the protocol. The start of a new cycle may be delayed on a weekly basis (assessed weekly) until recovery of toxicity to a level allowing continuation of therapy. If toxicity persists after a 2-week cycle delay that is related to 1 specific drug (eg, vincristine, doxorubicin), then the offending drug should continue to be withheld and the new cycle started with the remaining drugs. If R-CHOP is delayed, treatment with study drug should be continued during the delay phase. If the study drug (ibrutinib/placebo) is delayed or withheld, R-CHOP treatment may be continued if clinically indicated.

EFFICACY EVALUATIONS

Disease response will be assessed according to the Revised Response Criteria for Malignant Lymphoma. Efficacy assessments will be performed using computed tomography (CT) scans of the neck, chest, abdomen, and pelvis with IV and oral contrast as indicated. Whole body positron emission tomography (PET) scan is recommended but not mandated at baseline, but is required at the end of treatment. Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT. Other sites of disease will be evaluated by radiological imaging, physical examination, or other procedures as necessary, including review of hematology and serum chemistry results. After 4 cycles, an interim response assessment will be performed to evaluate progression for each subject. After the end of treatment (at least 3 weeks, preferably 6-8 weeks after last dose of R-CHOP), all subjects will also have an efficacy assessment. During the follow-up phase, all subjects without disease progression including those subjects who discontinue study treatment prior to progressive disease (PD) will have efficacy assessments every 16 weeks in the first 24 months, then every 24 weeks until PD, the clinical cutoff for the primary endpoint, or up to 5 years, whichever occurs first. After that, CT may be performed as clinically indicated (at the discretion of the investigator) per local standard of care. Radiological and PET scans performed prior to the database lock for the final analysis of EFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary.

PHARMACOKINETIC EVALUATIONS

In both treatment arms, sparse samples for the development of a population-based pharmacokinetic approach will be collected from all subjects from selected sites and evaluated for ibrutinib and potentially for PCI-45227. It is estimated that 200 subjects on ibrutinib are needed to adequately assess this. Collection of pharmacokinetic samples will stop when this cutoff point has been reached (or earlier or later at the sponsor's discretion). Pharmacokinetic parameters include oral plasma clearance, area under the plasma concentration time curve, minimum observed plasma concentration, maximum observed plasma concentration, and others if needed.

BIOMARKER EVALUATIONS

Tumor (from biopsy samples) will be evaluated in all subjects to identify markers predictive of response to ibrutinib. Paraffin-embedded, formalin-fixed tumor tissue or cells isolated from blood collections may also be subjected to RNA analysis (eg, GEP, quantitative reverse transcription [qRT]– polymerase chain reaction [PCR]) or somatic mutational analysis (eg, MiSeq, ExomeSEQ) from all subjects entered within this study. Comparison of IHC results may be made to transcriptomic or genomic data from matching tumor or blood to correlate molecular subtype and mutational status. Gene expression profiling and mutational analysis may also be utilized to identify other signaling pathway markers that may correlate with response to treatment (eg, CD79B, TP53, MLL2, CARD11, MYD88,) or other pathways/markers that may be up-regulated in the non-GCB subtype of DLBCL (eg, IL-6/STAT3). Other prognostic markers that may be analyzed include BCL-2 expression and C-MYC rearrangement. In addition, minimal residual disease assessment may be done on serum samples collected at the End-of-Treatment Visit and during the Posttreatment phase up to 24 months.

SAFETY EVALUATIONS

Regular periodic medical evaluations will be conducted including adverse event monitoring, physical examination, vital signs (temperature, heart rate, and blood pressure), weight evolution, concomitant medication usage, and performance status evaluation. Hematology and serum chemistry tests will be

performed at regular intervals. A baseline electrocardiogram and left ventricular ejection fraction measurement by multiple-gated acquisition scan or echocardiography is required in all subjects. Major hemorrhage has been identified as an adverse event of special interest and will require enhanced reporting and data collection. Data will also be collected on new malignant tumors occurring during study treatment and during any protocol-specified follow-up periods, including post-progression follow-up for overall survival.

STATISTICAL METHODS

The primary endpoint of the study is EFS, defined as the duration from the date of randomization to the date of disease progression, relapse from CR as assessed by investigator, initiation of subsequent systemic antilymphoma therapy for either PET-positive or biopsy-proven residual disease upon completion of at least 6 cycles of R-CHOP therapy, or death, whichever occurs first. Assuming 40% and 50% of the patients will be cured in the control (placebo+R-CHOP) and treatment (ibrutinib+R-CHOP) arms, respectively, and the hazard ratio of treatment over the control is 0.75 in the uncured subjects and the median EFS for the uncured subjects in the control arm is 12 months, approximately 419 EFS events will be observed, with 800 subjects (400 subjects in each arm) to be enrolled in 27 months and a follow-up period of 30 months after the 800th subject is randomized. The study is expected to maintain at least 90% power, with statistical significance at the overall alpha level of 0.025 (1-sided). The primary endpoint EFS will be analyzed using data from the Intent-to-Treat (ITT) population (defined as all subjects randomized into the study and classified according to assigned treatment arm) and the ABC population (identified by GEP). The alpha allocation for the ITT and ABC populations will be based on Song and Chi method (details provided in the Statistical Analysis Plan). The stratified log-rank test will be used as the primary analysis for treatment comparison. In case there is strong evidence of crossing hazard, other test statistics such as Rényi statistics may be used. Secondary endpoints include PFS, CR rate, overall survival, time-to-worsening in the Lym subscale of the FACT-Lym, pharmacokinetics, and safety. An independent Data Monitoring Committee (DMC) will be commissioned for this study to review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study in accordance with the DMC charter.

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Universal Trial Number: U1111-1139-6222

Table 1: Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis

	Pretreatment Phase	Active Treatment Phase (1 Cycle=21 days ±2 days)		Posttreatment Follow-up Phase	
	Screening[a]	**Active Treatment**	**Early Withdrawal/ End-of-Treatment Visit[b]**	**Prior to PD (CT Q16 wks [±7 d from last CT] first 24 mos; then every Q24wks [±10 d]) until PD or CCO for the Primary Endpoint Analysis**	**After PD (Q16 wks [±7 d])**
	≤30 d before randomization	Day 1 of each cycle			
Procedures					
Informed consent	X				
Paraffin-embedded tumor tissue and local pathology report[c]	X				
Fresh tissue biopsy			X (at PD, if feasible)		
Eligibility criteria review[c]	X				
Demographics/medical history/physical examination	X				
Limited physical examination[d]; vital signs (temperature, HR, BP)[e]	Vital signs	X[e]	X	Limited PE only	
ECOG performance status	X		X		
Height, weight, BSA	Height, weight	Weight, BSA[e]	Weight only		
ECG and echocardiogram or MUGA scan[f]	X				
AEs/concomitant medications	<---Continuous from informed consent to 30 d after the last dose of study treatment--->				
Disease Evaluations					
CT (neck, chest, abdomen, and pelvis)[g]	X[h]	End of Cycle 4 only[i]	X (at least 3 wks after last dose of R-CHOP; 6-8 wks preferred)[i]	X (for up to 5 years, then only as clinically indicated)	
Whole body FDG-PET scan	X[h]		X (at least 3 wks after last dose of R-CHOP; 6-8 wks preferred)[i]		
Bone marrow aspirate and biopsy	X[h]		X (if bone marrow positive at baseline)[i]		
PRO (FACT-Lym, EQ-5D-5L)[j]		X	X	X	X[k]
Survival status/subsequent antilymphoma therapy				X	X
Laboratory Assessments					
Hematology (see Section 9.5)	X	X (weekly)[l]	X		
Coagulation (aPTT, INR/PT)	X				
Serum chemistry (see Section 9.5)[m]	X	X[l]	X		
Hepatitis B and C serology	X[n]				
Serum β-hCG or urine pregnancy test	X[l]		X		
Beta-$_2$ microglobulin/serum immunoglobulin	X[l]		X	X (once; done at time of the first follow up CT)	
PK samples in subset of subjects (see Section 9.3.1)[o]		Cycles 1, 2, and 3			

	Pretreatment Phase	Active Treatment Phase (1 Cycle=21 days ±2 days)		Posttreatment Follow-up Phase	
	Screening[a]	**Active Treatment**	**Early Withdrawal/ End-of-Treatment Visit[b]**	**Prior to PD (CT Q16 wks [±7 d from last CT] first 24 mos; then every Q24wks [±10 d]) until PD or CCO for the Primary Endpoint Analysis**	**After PD (Q16 wks [±7 d])**
	≤30 d before randomization	Day 1 of each cycle			
Blood samples for biomarker evaluations		Cycle 1[p]	X[p]	X[p]	
Drug Administration (within 72 hours of randomization)					
R-CHOP		See Dose and Administration Table 2			
Dispense study drug/check drug accountability		X			
Study drug: Arm A: placebo (4 capsules) Arm B: ibrutinib 560 mg (4 capsules)		Continuous until PD, initiation of subsequent antilymphoma therapy, unacceptable toxicity, withdrawn, or completion of 6 or 8 cycles (as pre-specified by the site), whichever occurs first			

AE=adverse event; aPTT=activated partial thromboplastin time; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; BP=blood pressure; BSA=body surface area; CCO=clinical cutoff; CR=complete response; CT=computed tomography; d=day; DLBCL=diffuse large B-cell lymphoma; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; EQ-5D-5L=EuroQol questionnaire; FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma; FDG=[18F]-fluorodeoxyglucose; hr=hour; HR=heart rate; IHC=immunohistochemistry; INR=international normalized ratio; IV=intravenous; LDH=lactate dehydrogenase; min=minutes; MRD=minimal residual disease; MRI=magnetic resonance imaging; mos=months; MUGA=multiple-gated acquisition scan; non-GCB=non-germinal center B-like DLBCL; PCR=polymerase chain reaction; PD=progressive disease; PE=physical examination; PET=positron emission tomography; PK=pharmacokinetic; PRO=patient-reported outcomes; PT=prothrombin time; Q=every; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI=Revised international prognostic index; wks=weeks.

[a] Steroids are permitted prior to randomization (up to 100 mg prednisone or equivalent) for a maximum of 10 days, only after the baseline imaging assessment, baseline laboratory assessments, baseline performance status assessment, and baseline R-IPI calculation are performed. Baseline laboratory assessments need to be repeated if performed more than 5 d prior to the first dose of study treatment.

[b] Early withdrawal=stopping treatment before 6 or 8 complete cycles of study treatment are given, depending on the number of cycles pre-specified by each site. If any component of R-CHOP is discontinued for toxicity, study drug may continue up to the pre-specified number of treatment cycles. EOT Visit is required for all subjects; should occur 30 d (+10 d) after the last dose of study treatment. If study drug is discontinued, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may continue. If a subject requires subsequent antilymphoma therapy between the last dose of study treatment and the EOT Visit, then this visit should be completed just prior to initiation of subsequent antilymphoma therapy.

[c] Biopsy sample (paraffin-embedded tumor tissue) for central pathology determination of the non-GCB subtype of DLBCL and supportive materials (local pathology report) for verification of DLBCL diagnosis is required before a patient is considered eligible and can be randomized into the study. Biopsy sample must be sent to the central pathology laboratory within 28 d prior to randomization, however; a biopsy extracted from a subject >28 d prior to randomization is permitted. Part of the tumor biopsy block will be used for biomarker studies. Bone marrow is not sufficient for confirmation of the non-GCB subtype.

[d] Limited physical examination includes all organ systems previously abnormal or involved with disease and documentation of any clinically relevant organ abnormalities. Lymphoma symptoms reported at Screening should be reviewed and recorded during the limited physical examination.

[e] BSA calculated and vital signs done prior to dosing on Day 1 of each cycle. If a subject experiences a >10% change in weight from the weight used in the previous BSA calculation, then BSA and dose should be recalculated.

	Pretreatment Phase	Active Treatment Phase (1 Cycle=21 days ±2 days)		Posttreatment Follow-up Phase	
	Screening[a]	**Active Treatment**	**Early Withdrawal/ End-of-Treatment Visit[b]**	**Prior to PD (CT Q16 wks [±7 d from last CT] first 24 mos; then every Q24wks [±10 d]) until PD or CCO for the Primary Endpoint Analysis**	**After PD (Q16 wks [±7 d])**
	≤30 d before randomization	Day 1 of each cycle			

[f] Echocardiography or MUGA scan is mandatory at Screening; may be repeated at any time during the study (using same modality), as clinically indicated, either at an assessment visit or unscheduled visit.

[g] CT may be performed with oral contrast only if the subject is intolerant of IV contrast agents. MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (see Section 9.2.1.1 for details). Evaluation of other sites of disease may be performed by radiological imaging, physical examination, or other procedures as necessary (should be performed throughout the study using same method of assessment per subject).

[h] CT, MRI, PET, and bone marrow biopsy/aspirate may be performed up to 60 d before randomization (PET at screening is recommended but not mandatory). Morphological (and IHC, if warranted) examination of bone marrow is required. For subjects with bone marrow involvement prior to treatment, bone marrow aspirate and biopsy must be repeated once during the study to confirm CR (preferably within 30 d of initial CR documentation). Bone marrow at Screening should be performed within 60 d prior to the first dose of study treatment.

[i] Response assessment window: ±7 d. Assessments can be repeated if clinically indicated to confirm response or progression.

[j] The PRO questionnaires (FACT-Lym and EQ-5D-5L) will be collected at the beginning of the clinic visits, preferably, before any procedures or physician interactions. The first FACT-Lym and EQ-5D-5L assessment will be administered prior to the first dose of study treatment.

[k] Following disease progression, sites should attempt to administer the EQ-5D-5L every 16 wks for 32 wks.

[l] For Cycle 1 Day 1 only, if Screening tests were performed within 5 d of first dose of study treatment, then clinical laboratory tests do not need to be repeated. For subsequent cycles, samples can be taken within 72 hours of the scheduled visit, provided that results are available before study treatment is given. Pregnancy test during Screening within 21 d of Cycle 1 Day 1 does not need to be repeated. 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.

[m] At Screening: sodium, potassium, creatinine, AST, ALT, total bilirubin, albumin, uric acid, LDH, and alkaline phosphatase. On Day 1 of each cycle starting with Cycle 2: sodium, potassium, creatinine, total bilirubin, uric acid, and LDH. Magnesium on Day 1 of Cycles 1 and 2. Biochemistry tests may be repeated as clinically indicated.

[n] Screening for hepatitis B and C will include the following evaluations: hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody. Subjects who test positive for hepatitis B surface antigen or hepatitis B core antibody must have hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Hepatitis B surface antigen positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) and be treated according to local guidelines. Hepatitis B core antibody positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) or undergo regular monitoring of hepatitis B virus DNA according to local guidelines. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active hepatitis B virus infection and for signs of hepatitis during and following anti-B-cell treatment, according to local guidelines. Consultation with a hepatitis specialist is also recommended. 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.

[o] Before dosing of study drug (ibrutinib or placebo capsules) on Day 1 of Cycles 1, 2, and 3, and postdose on Cycles 1 and 2 at 1 hr (window 45 to 75 min), 2 hrs (window 1.5 to 2.5 hrs), and 4 hrs (window 3.5 to 6 hrs) after dosing.

[p] Day 1 of Cycle 1 (may be collected up to 5 days), at the time of disease progression, or the EOT Visit for subjects who discontinue study treatment without disease progression. In addition, MRD assessment may be done on serum samples collected at the EOT Visit and during the Posttreatment phase up to 24 months.

R-CHOP will be administered within 72 hours of randomization to subjects in both treatment arms as background therapy according to the following schedule (21 days per cycle) (Table 2):

Table 2: Dose and Administration Schedule for R-CHOP

		R-CHOP Regimen[a]					
Drug	Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6 to 21
Rituximab	375 mg/m^2 IV	X					
Cyclophosphamide	750 mg/m^2 IV	X					
Doxorubicin	50 mg/m^2 IV	X					
Vincristine	1.4 mg/m^2 IV (maximum total of 2 mg)	X					
Prednisone (or equivalent)[b]	100 mg orally	X	X	X	X	X	

IV=intravenously; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

[a] Six or 8 cycles per treatment arm, depending on the number of cycles pre-specified by each site. The components of the R-CHOP regimen can be given over 2 days.

[b] In regions where prednisone is not marketed or available, prednisolone will be used.

Table 3: Time and Events Schedule – After the Clinical Cutoff for the Primary Endpoint Analysis

	Posttreatment Follow-up Phase
Procedures	
Survival status (physician visit or telephone contact)	Every 24 weeks ±14 days until end of study.[a]
PRO (EQ-5D-5L)	Collect at 24 and 48 weeks ±14 days for those subjects who have not progressed at the time of clinical cutoff (ie, 2 times after the clinical cutoff for the primary endpoint analysis)
Progressive disease[b]/subsequent antilymphoma therapy	Every 24 weeks ±14 days until end of study (document progressive disease and subsequent antilymphoma therapy dates, if applicable)
New malignancies	Every 24 weeks ±14 days until end of study
Adverse events or serious adverse events and associated concomitant medications, if related to study treatment	Every 24 weeks ±14 days until end of study

EQ-5D-5L=EuroQol questionnaire; PRO=patient-reported outcomes

[a] The Posttreatment Follow-up Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first. The end of study is defined as when 50% of the randomized subjects have died or 5 years after the last subject is randomized or the sponsor terminates the study, whichever comes first.

[b] Radiologic disease evaluations may be performed as clinically indicated (at the discretion of the investigator) per local standard of care after the clinical cutoff for the primary endpoint analysis.

ABBREVIATIONS

ABC	activated B cell-like subtype of DLBCL
ACVBP	adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-last}	area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration
β-hCG	beta-human chorionic gonadotropin
BCR	B-cell receptor
BR	bendamustine + rituximab
BSA	body surface area
BTK	Bruton's tyrosine kinase
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL/F	oral plasma clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CYP	cytochrome P450
Cys	cysteine
DA-EPOCH-R	dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab
DNA	deoxyribonucleic acid
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
eDC	electronic data capture
EFS	event-free survival
EQ-5D-5L	EuroQol questionnaire
E_{max}	maximum obtainable effect
FACT-G	Functional Assessment of Chronic Illness Therapy-General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCR	fludarabine, cyclophosphamide, and rituximab
FDG	[18F] fluorodeoxyglucose
GCB	germinal center B cell-like subtype of DLBCL
GCP	Good Clinical Practice
GEP	gene expression profiling
GERD	gastroesophageal reflux disease
GI_{50}	50% growth inhibition
GTD	greatest transverse diameter
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	[redacted]
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin

IHC	immunohistochemistry
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
ITT	Intent-to-Treat population
IV	intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-κB	nuclear factor-kappa B
NHL	non-Hodgkin's lymphoma
Non-GCB	non-germinal center B cell-like subtype
ORR	overall response rate
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PLCγ	phospholipase C gamma
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
qRT	quantitative reverse transcription
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-IPI	Revised International Prognostic Index
RNA	ribonucleic acid
SET	Study Evaluation Team
SJS	Stevens-Johnson Syndrome
SPD	sum of the product of the diameters
$t_{1/2}$	half-life
T_{max}	time of maximum concentration
TTW	time to worsening
ULN	upper limit of normal
U.S.	United States
Vss/F	oral volume of distribution at steady state

1. INTRODUCTION

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is a first-in-class, potent, orally administered, covalently-binding, small molecule Bruton's tyrosine kinase (BTK) inhibitor 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 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. Phase 1 and 2 studies suggest that ibrutinib may be less active in subjects with germinal center B cell-like (GCB) diffuse large B-cell lymphoma (DLBCL), with an acceptable safety profile. Ibrutinib and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used.

1.1. Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma is an aggressive, although potentially curable, disease. Patients typically present with a large, fast growing mass; eg, an enlarged lymph node.[50] Only 30% to 55% of patients achieve durable cure;[14] the remaining patients ultimately die of the disease despite standard chemotherapy treatment. Chances of survival are reduced for patients with a disease onset on or after the age of 60 years, increased lactate dehydrogenase (LDH) levels (above normal limits), Eastern Cooperative Oncology Group performance status grade of ≥2, Stage III or IV disease, and more than 1 extra nodal disease site.[50]

Diffuse large B-cell lymphoma accounts for approximately 30% to 58% of all new cases of non-Hodgkin's lymphoma (NHL) diagnosed annually worldwide.[49] The incidence of DLBCL is approximately 23,911 patients in the United States (U.S.), 16,817 patients in the G5 countries (Germany, France, United Kingdom, Italy, and Spain), and 10,636 patients in Japan.[30,23] The average age at diagnosis is 64 years, with men slightly more affected then women.[50] For most patients, the origin of DLBCL is unknown. Factors thought to confer increased risk include immunosuppression and environmental chemicals. A variety of chromosomal alterations have been described in DLBCL. The most common abnormality involves alterations of the BCL-6 gene at the 3q27 locus, which is critical for germinal center formation. A substantial number of DLBCL cases have complex karyotypes.[16]

1.1.1. Standard Treatment for Diffuse Large B-Cell Lymphoma

Worldwide, the currently accepted standard regimen for frontline treatment of patients with DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Several studies have found the addition of rituximab to CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like chemotherapies significantly improve the clinical outcome of patients with DLBCL.[6,44,18,36] A randomized study of CHOP versus R-CHOP was performed in 398 newly diagnosed DLBCL patients, 60 to 80 years of age.[6] The rate of complete response (CR) was significantly higher in the group that received R-CHOP compared with the group that received CHOP alone (76% vs. 63%; p=0.005). With a median follow up of 2 years, event-free survival (EFS) was 57% in the R-CHOP group and 38% in the CHOP group. Results from the 10-year analysis confirmed the benefit of the addition of

rituximab to CHOP (10-year progression-free survival [PFS]: 36.5% vs. 20% for R-CHOP and CHOP, respectively; 10-year overall survival: 43.5% vs. 27.6%, respectively).[7] A pivotal Phase 3 study of CHOP versus R-CHOP with a second randomization to rituximab maintenance or observation in untreated patients 60 years and older with DLBCL also clearly showed that R-CHOP chemotherapy significantly prolonged failure-free survival in older DLBCL patients.[18] This study also showed that after R-CHOP, no benefit was provided by rituximab maintenance. The above 3 studies have established R-CHOP as the standard therapy for DLBCL.

Several other combination therapies have also been tested including DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab),[54] ACVBP (adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone; ie, intensive CHOP-like),[48,40] and 14-day CHOP,[36] but R-CHOP remains the current standard of care.[32]

1.1.2. Classification by Cell of Origen in Diffuse Large B-Cell Lymphoma

From both biological and clinical perspectives, DLBCL is a heterogeneous disease. To understand further the heterogeneity of this disease, gene expression profiling (GEP) has been used to investigate the different possible cellular origins of DLBCL. In 2000, Alizadeh and colleagues,[1] using DNA microarrays, have identified 2 molecularly distinct forms of DLBCL that had gene expression patterns indicative of different stages of B-cell differentiation. One type expressed genes characteristic of germinal center B-cells (`germinal center B cell-like DLBCL' [GCB]); the second type expressed genes normally induced during in vitro activation of peripheral blood B-cells (`activated B cell-like DLBCL' [ABC]). Patients with GCB DLBCL had a significantly better overall survival than those with ABC DLBCL.[1]

The 2002 Lymphoma/Leukemia Molecular Profiling Project used DNA microarrays to analyze biopsy samples of DLBCL from 240 patients, and found that the better survival rate for the GCB subtype was independent of clinical International Prognostic Index (IPI) risk.[43] Classification of DLBCL has also been shown to be clinically applicable by using a differential immunostaining method comprised of BCL-6, CD10, and MUM-1 antigens and an associated algorithm.[19] Various studies have shown that this classification, on the basis of the cell of origin, is an important independent prognostic factor for patients who are treated with CHOP or CHOP-like chemotherapy.[19,2,51] Additional biomarkers, such as BCL-2 overexpression, have been shown to be significant prognostic factors in ABC DLBCL but not in GCB DLBCL.[24] Some researchers have questioned the value of these prognostic indicators, given that adding rituximab to standard chemotherapy appeared to eliminate the prognostic value of the immunohistochemistry (IHC)-defined GCB and non-germinal center B cell-like (non-GCB) subtypes of DLBCL.[33] However, recent large, retrospective studies have since confirmed the prognostic importance of subclassification of DLBCL on the basis of the cell of origin even in rituximab-treated patients.[17] One study documented that, for patients treated with R-CHOP, the GCB subgroup had a significantly better 3-year overall survival than the non-GCB subgroup (85% versus 69%; p=0.032).[17] The largest dataset to date includes 475 subjects treated with R-CHOP who were successfully subclassified using various IHC algorithms (including Hans), that showed high

concordance (86.3% to 92.6%) with GEP. Subjects stratified into GCB and non-GCB groups using IHC had significantly different 5-year PFS rates.[52]

1.2. Investigational Product Name and Description

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

1.3. Summary of Relevant Nonclinical and Clinical Data

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

1.3.1. Nonclinical Data

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.[34] In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-C gamma (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase.[22] Ibrutinib inhibited the proliferation of cell lines derived from DLBCL patients with a median effective concentration of 1 or 2 nM.

1.3.2. Clinical Pharmacokinetic Data

In vitro preclinical data show that ibrutinib is metabolized primarily by CYP3A. Its bioavailability is variable and relatively low (data on file). Study PCI-32765CLL1002 was an open-label study with a drug-drug interaction cohort of 18 healthy men, in which ibrutinib was administered alone at a 120-mg dose or in combination with ketoconazole at a 40-mg dose. Results demonstrated that ketoconazole, a strong cytochrome P450 (CYP)3A inhibitor, increased ibrutinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration [$AUC_{0\text{-last}}$]) by 29- and 24-fold, respectively. Terminal half-life was not increased. Guidance on concomitant use of ibrutinib/placebo with CYP3A inhibitors or inducers is provided in Section 8.2.1.

Study PCI-32765CLL1004 was a mass-balance study in 6 men in which ibrutinib was administered as a 140-mg solution admixed with ^{14}C-ibrutinib. Preliminary results from Study PCI-32765CLL1004 showed approximately 90% of radioactivity was excreted within 168 hours after administration, with less than 10% accounted for in urine and the remainder in feces. A negligible fraction was excreted as unchanged drug.

Summary of Human Pharmacokinetics

Extensive pharmacokinetic sampling and evaluation have been performed in approximately 250 subjects receiving ibrutinib across 5 of the above mentioned clinical studies: PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, and PCYC-1109-CA and results are briefly summarized below.

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day, area under the plasma concentration-time curve (AUC) values for ibrutinib increased with increasing dose, but with considerable overlap in values. The coefficient of variation for the AUC ranged from 60% to 107% across 3 studies (Studies PCYC-04753, PCYC-1102-CA, and PCYC-1109-CA). The mean half-life ($t_{1/2}$) of ibrutinib across 4 clinical studies ranged from 4.3 to 8.9 hours, with a median time of maximum concentration (T_{max}) of 2 hours.

Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227. The metabolite to-parent AUC ratio ranged from 1.4 to 3.2. Consistent with the profile observed for ibrutinib, there was no apparent accumulation of the metabolite PCI-45227 in the plasma after repeated daily oral dosing with ibrutinib. PCI-45227 is a reversible inhibitor of BTK with approximately 10% of the inhibitory potency of ibrutinib. The effect of renal impairment on drug clearance in humans is not known at this time. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration of 140 mg ibrutinib under fasted conditions, the AUC_{last} of ibrutinib increased 2.7-, 8.2-, and 9.8-fold in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment compared to subjects with normal liver function. The safety of ibrutinib has not been evaluated in patients with hepatic impairment.

Pharmacokinetic and Pharmacodynamic Relationship

Ibrutinib binds covalently and irreversibly to Cys-481 near the BTK active site and inhibits the enzymatic activity of purified BTK with a half maximal inhibitory concentration (IC_{50}) of 0.5 nM. In Study PCYC-04753, the BTK active-site occupancy by ibrutinib was measured in the peripheral blood samples collected before and at 4 and 24 hours after administration of ibrutinib for each subject on Days 1, 8, and 28. The 24-hour samples were collected before dose administration the next day. Bruton's tyrosine kinase remained fully occupied by ibrutinib (≥90% occupancy) for at least 24 hours in all subjects in Cohorts 2 through 5 (2.5 to 12.5 mg/kg/day) and for the 560 mg continuous dosing cohorts. Although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dosing.

The relationship between the averaged BTK occupancy at 4 and 24 hours postdose (trough exposure) and the Day 1 area under the plasma concentration versus time curve from 0 to 24 hours [AUC_{0-24}] for ibrutinib can be described by a simple maximum obtainable effect (E_{max}) model. 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 AUC_{0-24} values ≥160 ng·h/mL. In Study PCYC-1104-CA, in which ibrutinib was administered to

subjects with relapsed/refractory MCL as a fixed dosage of 560 mg/day, 96% of the subjects retained steady-state ibrutinib AUC value >160 ng·h/mL. This result indicates that a dose of 560 mg/day is adequate to achieve exposures yielding full BTK active-site occupancy in most patients with MCL. In addition, this dose was used to establish initial efficacy evaluations in Phase 1 and 2.

1.3.3. Clinical Efficacy of Ibrutinib in Diffuse Large B-cell Lymphoma

Efficacy results from Studies PCYC-04753 and PCYC-1106-CA demonstrate that ibrutinib has robust activity as a single agent in subjects with relapsed or refractory DLBCL, with possible lower response rates in subjects with the GCB subtype.

1.3.3.1. Study PCYC-04753

This is a completed, Phase 1, multicenter, open-label, dose escalation study in 66 subjects with recurrent NHL. The objectives included studying the safety profile of ibrutinib, identifying the maximum tolerated dose (MTD) and optimal dosing schedule, and characterizing efficacy, pharmacokinetics, and pharmacodynamics. A minimum of 6 subjects per cohort received 1 of 5 escalating dose levels of ibrutinib between 1.25 and 12.5 mg/kg for 28 consecutive days in a 35-day cycle, with the objective of escalating 3 dose levels above that which achieved full BTK occupancy based on the fluorescent probe assay. Two additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg without a 7-day rest and a fixed continuous dose of 560 mg/day.

Full BTK occupancy was achieved with doses at ≥2.5 mg/kg/day; consequently, per protocol, 12.5 mg/kg/day was the highest dose cohort evaluated. There were 2 dose-limiting toxicities (DLTs) (Grade 2 neutropenia [2.5 mg/kg/day] and Grade 3 hypersensitivity [8.3 mg/kg/day]); these events occurred in different dose cohorts, with neither in the highest-dose nor a continuous dosing cohort. The MTD of ibrutinib in subjects with B-cell malignancies was not established in this study.

Five of 15 subjects with DLBCL (33%) achieved objective responses, 2 CRs and 3 partial responses (PRs). The median time on treatment was 8 weeks (range: 2 to 98 weeks). Median PFS was 2.5 months (range: 0.7 to 4.6 months) and the median follow-up time was 3.5 months (range: 0.8 to 22.5 months).

1.3.3.2. Study PCYC-1106-CA

This is a Phase 2, multicenter, open-label, single-arm study in subjects with relapsed or refractory DLBCL. Subjects are enrolled and retrospectively assigned to 1 of 2 cohorts by subtype: ABC versus GCB as per central GEP. All subjects have received a continuous fixed dose of ibrutinib 560 mg/day. The objectives include studying the efficacy of ibrutinib in DLBCL and the safety of this dosing regimen.

The study has completed enrollment. Seventy subjects were enrolled with a median age of 63 years (range: 28 to 92 years) and a median of 3 prior systemic therapies (range: 1 to 7). Median time from diagnosis was 19 months. In a subset of samples, a comparison of the central IHC by Hans algorithm to the GEP algorithm that was used in this Phase 2 clinical study

(ie, Sensation algorithm; 200 genes) was performed (unpublished data on file).[55] Non-GCB by central IHC, blinded to the GEP assignment and clinical data, had a 92% concordance (12/13) with GEP. For the 60 response evaluable subjects, the overall response rate (ORR) was 21.7% (13/60 subjects). Median PFS was 1.64 months (Table 4).[55] In the ABC subtype, ORR was 40% (10/25 subjects; 95% confidence interval [CI]: 21% to 61%), CR 8% (2/25 subjects), and PR 32% (8/25 subjects). Only 1 PR (1/19 subjects; 5.3%) was observed in the GCB subtype and none in unclassifiable cases. Thus, while the 2 subgroups were clinically not well balanced, ibrutinib showed less activity in the GCB DLBCL subtype (p=0.0126, Fisher's exact test).[55]

Table 4: Study PCYC-1106-CA Efficacy Results

	ABC subtype (n=29)	GCB subtype (n=20)	Unclassifiable[a] (n=16)	Unknown[b] (n=5)	Total (N=70)
Evaluable for Response	25	19	13	3	60
PP ORR (CR+PR)	10 (40%)	1 (5.3%)	0	2 (66.7%)	13 (21.7%)
CR	2 (8%)	0	0	1 (33.3%)	3 (5%)
PR	8 (32%)	1 (5.3%)	0	1 (33.3%)	10 (16.7%)
PFS (months)	2.5	1.28	0.95	NR	1.64

ABC=activated B-like DLBCL; CR=complete response, GCB=germinal center B cell-like DLBCL; NR=not reached; ORR=overall response rate; PFS=progression-free survival; PP=per-protocol population; PR=partial response

[a] Gene expression profiling performed, but not assignable to ABC or GCB subtypes.

[b] Gene expression profiling not yet performed or tissue not available.

1.3.3.3. Post hoc Analysis

A post hoc analysis of pooled data from the DLBCL expansion cohort of Study PCYC-04753 and Study PCYC-1106-CA was conducted. The effect of a prior response to chemotherapy on subsequent response to ibrutinib was assessed for all subjects with DLBCL and for subjects in 2 subsets of DLBCL, ie, the ABC DLBCL and non-ABC DLBCL subsets. More subjects in the ABC DLBCL subset who were chemo-sensitive had a response (11/14 subjects, 78.6%) compared with the chemo-sensitive non-ABC DLBCL subset (4/16 subjects, 25.0%). Fewer subjects with ABC DLBCL who were chemo-refractory (defined as failure to achieve a response to the last prior chemotherapy regimen, ie, a regimen with at least 2 chemotherapeutic agents) had a response (4/25 subjects, 16%), but the response was still favorable as compared with the chemo-refractory non-ABC DLBCL subset (0/25 subjects, 0%). Based on these results, ibrutinib appears to be more active in subjects with chemo-sensitive DLBCL. Therefore, use of ibrutinib in earlier lines of therapy and in the non-GCB subtype of DLBCL may have the greatest clinical effect.

1.3.3.4. Study PCI-32765DBL1002

This is a multicenter, dose-escalation and expansion study in subjects with newly diagnosed CD20-positive B-cell NHL including DLBCL, follicular lymphoma, and MCL. Thirty-three subjects have been enrolled in this study of whom 24 subjects have DLBCL; 18 subjects with newly diagnosed DLBCL were treated at the recommended Phase 2 dose (ibrutinib 560 mg daily) in combination with R-CHOP.

In the dose-escalation phase of this study, subjects were assigned to cohorts of increasing oral daily doses of ibrutinib 280 mg (n=7), 420 mg (n=4), and 560 mg (n=6) administered in combination with R-CHOP. A Study Evaluation Team (SET) reviewed all available data upon completion of the first cycle for all subjects at each dose cohort to determine DLTs. After the recommended Phase 2 dose was determined (560 mg), 16 subjects with newly diagnosed DLBCL were enrolled into the expansion cohort. Subjects are allowed to continue to receive ibrutinib and R-CHOP up to a maximum of 6 cycles. The study will end 1 year after the last subject has completed the End-of-Treatment Visit. The data summarized below are preliminary and are subject to change upon study completion and data review.

Preliminary response data based on the final analysis suggest activity with this regimen, with 18/18 (100%) evaluable subjects with DLBCL treated at a dose of 560 mg ibrutinib + R-CHOP achieving a response (14 CRs and 4 PRs; Table 5). While these data are encouraging, they must be interpreted in the context of the small sample size, the immaturity of the data, and the known response rate of background therapy.

Table 5: Preliminary Response Data (Study PCI-32765DBL1002)

		DLBCL			MCL			FL		
Dose level	Total	(n)	CR	PR	(n)	CR	PR	(n)	CR	PR
280 mg	7[a]	2	2		3	3		1		1
420 mg	4	2	2		0			2	1	1
560 mg (dose escalation)	6[b]	3	1	2	2	1	1	0		
RP2D (560 mg, expansion)	16[c]	15	13	2	0			0		

CR=complete response; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; PR=partial response; RP2D=recommended Phase 2 dose.

[a] One subject not evaluable for response because the subject refused further treatment after the initial dose (only 1 dose of 280 mg taken).

[b] One subject not evaluable for response, the subject refused further follow up after discontinuation of therapy (Cycle 2 Day 8) and was withdrawn from the study.

[c] One subject not evaluable for response due to serious adverse event (rituximab reaction); subject discontinued the study before ibrutinib exposure.

1.3.4. Clinical Safety of Ibrutinib

As of 6 April 2015, 1071 subjects have been treated with ibrutinib monotherapy 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.

1.3.4.1. Monotherapy Studies

1.3.4.1.1. 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, >400000/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.

1.3.4.1.2. 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 8.2.4.

Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. 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 8.2.3.

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 6.2.6.

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 medication 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, angioedema have been reported.

Tumor Lysis Syndrome

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

1.3.4.2. Combination Therapy Studies

The safety of ibrutinib administered as combination therapy to 130 subjects was evaluated in 3 clinical studies: Studies PCYC-1108-CA, PCYC-1109-CA, and PCI-32765DBL1002. In Study PCYC-1108-CA, ibrutinib was administered in combination with either the FCR (fludarabine, cyclophosphamide, and rituximab) or the BR chemotherapy regimen (bendamustine and rituximab). In Study PCYC-1109-CA, ibrutinib is administered in combination with the monoclonal antibody ofatumumab in patients with relapsed and refractory CLL. In Study PCI-32765DBL1002, ibrutinib is administered in combination with standard R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone).

Across these combination studies, the most common adverse event has been diarrhea (47.7%), nausea (33.1%), infusion related reaction (29.2%), and fatigue (26.2%). Neutropenia (24.6%) has been the most common hematologic toxicity, followed by anemia (20.0%) and thrombocytopenia (19.2%).

Adverse events that were Grade 3 or higher in severity were reported in 57.7% of subjects. The most common have been hematologic: neutropenia (21.5%), anemia and thrombocytopenia (7.7% each), and febrile neutropenia (6.2%). Pneumonia (7.7%) was the most frequently reported nonhematologic Grade 3 or higher adverse event.

Overall, 36.2% of treated subjects have experienced at least 1 serious adverse event. The most commonly reported serious adverse events were febrile neutropenia and pneumonia (6.2% each), cellulitis (3.8%), atrial fibrillation (3.1%), and dehydration and dyspnea (2.3% each).

1.3.4.2.1. Preliminary Results From Study PCI-32765DBL1002

Preliminary results from an ongoing Phase 1b study in subjects with newly diagnosed NHL, Study PCI-32765DBL1002, are summarized below with a data cutoff of 08 July 2013.

The following DLTs were reported during the dose-escalation phase: at the lowest dose level (280 mg), 2 DLTs in 2 subjects were reported: Grade 3 syncope that triggered an expansion of the cohort to 7 subjects and Grade 3 peri-orbital cellulitis. No DLTs were reported at the 420-mg dose. Another DLT was reported at the highest dose (560 mg) in a subject who had Grade 2 gastritis (requiring 7 days dose interruption), and triggered dose cohort expansion. The subject had a history of well-controlled gastrointestinal disorders (gastroesophageal reflux disease

[GERD] and irritable bowel syndrome). The SET agreed further enrollment of 2 additional subjects at the 560 mg/day dose level, thus expanding the cohort to 6 evaluable subjects. Once all 6 subjects were evaluated through the first cycle and no additional DLTs were observed, the SET re-convened and confirmed that the recommended Phase 2 dose be set at 560 mg ibrutinib+R-CHOP, and enrollment of the expansion phase for subjects with newly diagnosed DLBCL proceeded.

Preliminary Safety Analysis

As of 08 July 2013, safety data are available for all 33 subjects; 32 subjects were treated with the ibrutinib + R-CHOP combination; 1 subject was enrolled but discontinued the study prior to ibrutinib exposure due to a rituximab reaction; 21 subjects (18 subjects with DLBCL, 2 subjects with MCL, and 1 subject with FL) have received the recommended Phase 2 dose. All 33 subjects experienced at least 1 treatment-emergent adverse event; the most common were neutropenia (67%), nausea (67%), thrombocytopenia (61%), vomiting (49%), anemia (36%), fatigue (30%), and diarrhea (30%). The most common treatment-emergent adverse events of Grade 3 or higher severity were neutropenia (61%), thrombocytopenia (21%), anemia (18%), and febrile neutropenia (15%). Serious Adverse Events were reported in 46% of all patients, and most common serious adverse events reported were febrile neutropenia (15%) and pyrexia (6%). All other SAEs were reported in 1 subject each. The incidence of neutropenia and febrile neutropenia reported to date is consistent with treatment with R-CHOP alone, which is has been reported at 19% for febrile neutropenia[35] and 62% for neutropenia.[20] The overall toxicity profile in this study is also consistent with the known profiles of R-CHOP and ibrutinib independently. Based on the interim data, there appears to be no new or unexpected toxicities or additive/synergistic effects of the combination ibrutinib+R-CHOP.

Preliminary Pharmacokinetic Results

Thirty-two subjects have received ibrutinib in combination with R-CHOP. The risks associated with ibrutinib and the dihydrodiol metabolite PCI-45227 as potential perpetrators of clearance mechanisms of concomitant medications were assessed based on literature review and pharmacokinetic measurements in the Phase 1b Study PCI-32765-DBL1002. It was concluded that enzymatic drug-drug interactions between ibrutinib or the dihydrodiol metabolite PCI-45227 and each of the 5 R-CHOP components were unlikely. To confirm this, vincristine pharmacokinetic was evaluated in Study PCI-32765DBL1002, as this drug was considered the most plausible drug-drug interaction target since CYP3A4 has been shown to be relevant for vincristine's systemic clearance. Preliminary PK analysis of a subset of subjects showed that there was no effect of ibrutinib co-administration on vincristine PK. For the other compounds of this combination chemotherapy regimen, clinical drug-drug interaction with ibrutinib is not expected. Co-administration of R-CHOP and ibrutinib did not affect ibrutinib exposures in a clinically meaningful way.

Dose Reductions

As of 08 July 2013, 5 of 21 subjects enrolled at the 560-mg dose level reported dose reductions of ibrutinib (preliminary data). One subject who had a DLT of gastritis (discussed above)

resulting in dose reduction started the second cycle at a reduced dose of 420 mg; the subject discontinued the study permanently on Cycle 2 Day 8 due to Grade 2 gastritis. The second subject had a dose reduction secondary to increased bleeding time (bleeding time was assessed by the Ivy method) without any clinical evidence of bleeding at Cycle 2 Day 1; bleeding time was prolonged for 25 minutes at Cycle 2 Day 1). The dose was reduced to 420 mg and the bleeding time was re-assessed 1 week later as prolonged for 8.5 minutes by the Ivy method. The subject continued on the 420 mg ibrutinib dose and completed 6 cycles of therapy. Two subjects had a dose reduction due to febrile neutropenia (dose reduced to 420 mg at Cycle 3 Day 1) and 1 of these subjects had a further dose reduction due to onset of fever that required hospitalization (Cycle 4 Day 1), both subjects completed 6 cycles of therapy; supportive therapy (growth factors) was given prior to the event for 7 and 8 days, respectively. Lastly, 1 subject required 2 dose reductions (Cycle 1 Day 8 and Cycle 2 Day 7) due to severe diarrhea that was controlled by anti-diarrheal therapy. The subject continued therapy at the reduced dose of 280 mg and is currently ongoing at Cycle 6.

For vincristine, dose reductions and discontinuations were reported in 11 of 33 subjects across all dose levels. With the exception of 1 subject who experienced sinus pain, neuropathy was the main reason for dose reduction of vincristine. Vincristine dose reductions occurred during Cycle 2 (n=1), Cycle 5 (n=4) and Cycle 6 (n=6). For prednisone, dose reductions were reported in 2 subjects treated at the recommended Phase 2 dose; the reported dose reduction was attributed to the local hospital administering 40 mg instead of 100 mg. For doxorubicin and cyclophosphamide, dose reductions were reported in 2 subjects enrolled at the highest dose level due to febrile neutropenia (both at Cycle 3 Day 1); both subjects completed 6 cycles of therapy.

1.3.4.3. Treatment Discontinuations

Sixty-two of the 506 subjects (12%) in the monotherapy population and 9 of the 130 subjects (7%) in the combination therapy population discontinued treatment due to an adverse event. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects for each event).

1.3.5. Background Therapy

R-CHOP, the currently accepted standard regimen for frontline treatment of patients with DLBCL worldwide, will be used as background therapy. For further information regarding rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone (or equivalent), refer to the local prescribing information.

1.4. Overall Rationale for the Study

Diffuse large B-cell lymphoma is the most common type of NHL and constitutes 30% to 58% of all lymphomas.[49] About half of patients diagnosed with DLBCL achieve long-term disease survival with a combination of rituximab and chemotherapy (R-CHOP).[6] However, a substantial number of patients remain inadequately treated or relapse after response to initial treatment.[13] Clinically, these patients appear to be older, present with high IPI scores, or may have bone

marrow involvement of the disease, characteristics that may in fact be surrogate markers of intrinsic molecular heterogeneity.[45,31]

It is increasingly appreciated that DLBCL is heterogeneous in terms of morphology, genetics, and biologic behavior. Immunohistochemistry and GEP are 2 of the assay platforms currently being used for determining cell of origin. Immunohistochemistry divides the population into 2 categories: GCB and non-GCB. Gene expression profiling platforms assign specimens into 1 of 3 diagnostic categories: GCB, ABC, or unclassified. Non-GCB comprises the categories of ABC and unclassified. Gene expression profiling identified GCB as the subtype with stronger predictive value for prognosis and response to R-CHOP.[1] Subsequent IHC studies have demonstrated that these GCB and non-GCB variants can be accurately predicted using a panel of only 3 immunostains.[19] The GCB subgroup, positive for CD10 and BCL-6, but negative for MUM1, has significantly better survival outcomes than the ABC group that is positive for MUM1.[19,43] Additional subtypes, such as primary mediastinal B-cell lymphoma (PMBL), are less common but genetically and clinically distinct.[43] Clinical studies with R-CHOP have shown the prognostic importance of subclassification of DLBCL, demonstrating that the GCB subgroup has a significantly better 3-year survival than the non-GCB subgroup (85% versus 69%; p=0.032).[17] High concordance between GEP and IHC now established central IHC as a practical process for screening patients in the clinical setting.[52]

The gene expression profiles for ABC DLBCLs are also notable for the high expression of target genes of the nuclear factor-kappa B (NF-κB) transcription factor.[9] The NF-κB pathway is important for normal intracellular signaling during cellular differentiation and immune responses.[9] However, the presence of high NF-κB activity in B-cell receptor (BCR) signaling, as seen in the ABC subtype of DLBCL, has been suggested to contribute to poor prognosis.[9,43] Conversely, the NF-κB pathway is essentially silent in the GCB subtype of DLBCL, making this pathway a unique target for the non-GCB subtype of DLBCL.[10] Targeted agents of the BCR pathway in non-GCB DLBCL may inhibit downstream activation of the NF-κB pathway specifically in populations where this pathway is activated.

Bruton's Tyrosine Kinase is a key component of the BCR-signaling cascade that can lead to activation of the NF-κB pathway. In vitro data suggest that the BTK inhibitor ibrutinib can kill ABC DLBCL cell lines with constitutively activated BCR signaling, but have no effect on ABC and GCB DLBCL cell lines that do not rely on constitutive BCR signaling.[10,47] These nonclinical data were corroborated by clinical results from the ABC-DLBCL cohort in PCYC-04753[47] and the PCYC-1106-CA study of ibrutinib in relapsed/refractory DLBCL,[55] suggesting that ibrutinib is active in subjects with DLBCL, with less activity in subjects with the GCB subtype. Interestingly, these data also suggest that ibrutinib shows superior activity among DLBCL patients who are still chemosensitive. Together, these findings suggest a potentially important role for ibrutinib as front-line treatment in the non-GCB subtype. Early data from an ongoing Phase 1 combination study shows that ibrutinib can be safely combined with R-CHOP. This study will evaluate whether ibrutinib in combination with R-CHOP improves the outcome in newly diagnosed patients with the non-GCB subtype, ABC subtype, or both subtypes of DLBCL.

At the time the study was designed and began enrolling in 2013, subjects with the non-GCB subtype of DLBCL were selected using the IHC method (not by GEP) because IHC was identified as a clinically viable and more widely available method. Immunohistochemistry, using various algorithms including the Hans algorithm, utilized commonly available FFPE tumor samples and was accepted worldwide as an approach to classify subjects into either the GCB and non-GCB subtype. In contrast, at that time GEP used freshly frozen tumor samples (there was no validated or reproducible GEP assay for DLBCL subtyping using commonly available FFPE tissue) and DNA microarrays, which made GEP an experimental approach with limited availability. Moreover, at that time GEP had a turnaround time of 2 to 3 weeks, which made the use of GEP challenging because many patients could not delay treatment until GEP results were available. Recently, however, standardized DLBCL cell-of-origin GEP assays [redacted] that can be performed on FFPE specimens with shorter sample turnaround times have become available. This new approach will allow for retrospective analysis of available tumor samples by GEP from subjects who were screened and selected for this study using IHC. The analysis of the treatment benefit of subjects with the ABC subtype by GEP was included as a secondary endpoint when this study was initiated.

This study will evaluate whether ibrutinib in combination with R-CHOP improves the outcome in subjects with newly diagnosed non-GCB DLBCL selected by IHC or in subjects with newly diagnosed ABC DLBCL identified by GEP or both patient populations.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

The primary objective is to evaluate if the addition of ibrutinib to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) prolongs event-free survival (EFS) compared with R-CHOP alone in subjects with newly diagnosed non-GCB subtype of DLBCL selected by IHC or in subjects with newly diagnosed ABC subtype of DLBCL identified by GEP or both patient populations.

Secondary Objectives

The secondary objectives are to:

- Evaluate PFS
- Evaluate CR rate
- Evaluate overall survival
- Evaluate patient-reported lymphoma symptoms and concerns as measured by the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
- Characterize the pharmacokinetics of ibrutinib and to explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information
- Evaluate the safety of ibrutinib when combined with R-CHOP

Exploratory Objectives

The exploratory objectives are to:

- Evaluate patient-reported outcomes (PRO), related to well-being and general health status, utilizing the FACT-Lym and EuroQol questionnaire (EQ-5D-5L)
- Explore the relationship between relevant biomarkers (eg, GEP, gene mutations) with clinical outcomes and mechanism of resistance

2.2. Hypothesis

Ibrutinib in combination with R-CHOP will prolong EFS compared with R-CHOP alone in subjects with newly diagnosed non-GCB DLBCL selected by IHC or in subjects with newly diagnosed ABC DLBCL identified by GEP or in both patient populations.

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 R-CHOP versus R-CHOP alone in subjects 18 years and older with newly diagnosed non-GCB DLBCL.

Approximately 800 eligible subjects will be randomly assigned in this study, with 400 subjects planned per treatment arm. Eligible subjects will be stratified by Revised IPI (R-IPI; 1-2 vs. 3-5 [Attachment 1]), region (U.S./Western Europe vs. Rest of World), and number of pre-specified treatment cycles per local practice (6 vs. 8 cycles) then randomized in a 1:1 ratio to receive either placebo+R-CHOP (Treatment Arm A) or 560 mg ibrutinib+R-CHOP (Treatment Arm B).

The study will include a Pretreatment (Screening) Phase, Active Treatment Phase, and a Posttreatment Follow-up Phase. Before any study related-procedure can be performed, all subjects must sign an informed consent form (ICF). Subjects will be evaluated for eligibility at Screening. Subjects must complete Screening procedures within 30 days before randomization, unless otherwise specified.

The Active Treatment Phase will extend from Day 1 Cycle 1 until study treatment discontinuation due to disease progression, initiation of subsequent antilymphoma therapy, unacceptable toxicity, withdrawn, or completion of study treatment. All subjects will receive R-CHOP as background therapy for 6 or 8 cycles per site preference (21 days per cycle). Sites may choose to administer 6 or 8 cycles of treatment based on local practice. Once the number of cycles is selected by the site, all subjects at individual sites are intended to receive the prespecified number of treatment cycles (6 or 8); no individual subject adjustment is permitted based on interim response. Study treatment administration begins on Cycle 1 Day 1 and ends on Day 21 of the last cycle, unless if the subject experiences unacceptable toxicity or disease progression.

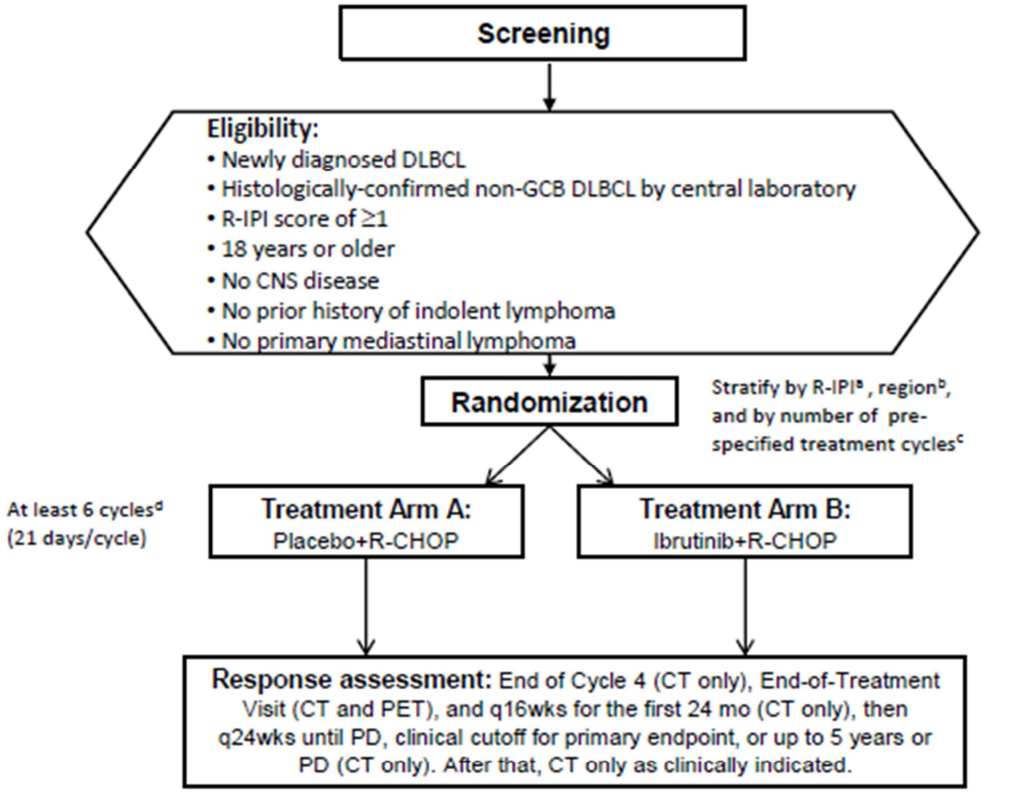
After 4 cycles, an interim response assessment will be performed to evaluate progression for each subject. Subjects with progressive disease (PD) or relapsed disease after CR will be discontinued from study treatment. Subjects who discontinue any component of R-CHOP without disease progression, will continue study drug (placebo or ibrutinib) until 6 or 8 cycles are completed (depending on the number of cycles pre-specified by each site), disease progression, or unacceptable toxicity, whichever occurs first. After completion of study treatment, subjects will undergo assessment of tumor response by computed tomography (CT) scan and positron emission tomography (PET) scan. Response criteria are based on the Revised Response Criteria for Malignant Lymphoma.[5] Subjects with PET-positive or biopsy-proven residual disease upon completion of at least 6 cycles of R-CHOP therapy are considered eligible to initiate subsequent antilymphoma therapy.

The Posttreatment Follow-up Phase will begin once a subject has completed study treatment. At the End-of-Treatment Visit, follow-up visits to assess for disease progression, will be required if study treatment is discontinued prior to PD and will be completed until PD, the clinical cutoff for the primary endpoint, or up to 5 years, whichever occurs first (see Time and Events Schedules; Table 1 and Table 3). After that, CT may be performed as clinically indicated (at the discretion of the investigator) per local standard of care. Subjects who discontinue study treatment for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule (Table 1). The Posttreatment Follow-up Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first. The end of study is defined as when 50% of the randomized subjects have died or 5 years after the last subject is randomized or the sponsor terminates the study, whichever comes first.

The investigator will evaluate sites of disease by radiological imaging, physical examination, or other procedures as necessary. At each site visit, subjects will undergo safety evaluations. Safety evaluations will include adverse event monitoring, physical examinations, vital signs, concomitant medication usage, and clinical laboratory parameters. In a subset of subjects, blood samples will be drawn for assessment of pharmacokinetic parameters.

Three clinical cutoffs are planned (see Section 9.1.5); the primary efficacy analysis of EFS will be based on investigator assessment. Radiological and PET scans performed prior to the database lock for the final analysis of EFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary. Available tumor samples will be retrospectively analyzed to identify the ABC DLBCL population using GEP. An independent Data Monitoring Committee (DMC) will be commissioned for this study. Refer to Section 11.10, Data Monitoring Committee, for details. A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study



CT=computed tomography; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; GCB=germinal center B-like cell; IHC=immunohistochemistry; mo=months; PD=progressive disease; PET=positron emission tomography; q=every; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI=revised international prognostic index; wks=weeks

[a] R-IPI score of 1-2 versus 3-5.

[b] U.S./Western Europe vs. Rest of World.

[c] Six versus 8 cycles.

[d] Sites will pre-specify 6 or 8 cycles prior to study start (no adjustment permitted once pre-specified).

3.2. Study Design Rationale

This is a Phase 3, randomized, double-blind, controlled study evaluating the addition of ibrutinib to the standard of care in non-GCB DLBCL. The study will recruit patients globally and is adequately powered to demonstrate an improvement of the ibrutinib combination over the standard of care. This study design is widely employed to obtain global regulatory approval of new treatments.

Randomization will be used to minimize bias in the assignment of subjects to treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints. Subjects will be stratified by R-IPI (1-2 vs. 3-5) score, a well-established prognostic index for patients with DLBCL; region; and number of pre-specified treatment cycles (6 vs. 8 cycles).

3.2.1. Study Population

The rationale for selecting the non-GCB DLBCL Intent-to-Treat (ITT) patient population in this study is, in part, based on results from Studies PCYC-04753 and PCYC-1106-CA suggesting that ibrutinib appears to be less active in subjects with GCB DLBCL (see Section 1.3.3). In addition, activity appears to be enhanced in the target population when subjects are chemosensitive.

3.2.2. Study Treatments

The 560 mg daily dose of ibrutinib was selected as the recommended dose in combination with R-CHOP for this study based on nonclinical data and clinical data from Studies PCYC-04753 and PCYC-1106-CA. See Section 1.3. The comparator in this study, R-CHOP, was selected as it is the standard of care (see Section 1.1.1).

The primary endpoint, EFS, has served as the basis for regulatory approval in DLBCL and represents a clinically meaningful improvement attributable to treatment in this subject population.[42,29] The FACT-Lym questionnaire will provide an assessment of the subject's own functional status, well-being, and lymphoma symptoms over time. The EQ-5D-5L assessment will provide estimates of utility to include in future cost effectiveness models.

The assessment of pharmacokinetics 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.

3.2.3. Biomarker Collection

Inhibition of BTK tyrosine phosphorylation by ibrutinib has been shown to abrogate downstream survival pathways (ERK1/2, PI3K, NF-κB, MAPK). Inhibition by ibrutinib also interferes with activation of integrins and chemokine networks leading to interference with adhesion, migration, and homing of malignant cells.[21,38] It is anticipated that subjects with alterations in BCR signaling components or activation of alternative signaling pathways, may have a different response to treatment. The biomarker evaluations within this study will identify biomarkers associated with response (and potentially resistance) to ibrutinib in subjects with non-GCB DLBCL.

4. SUBJECT POPULATION

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

Section 11.3, Sample Size Determination. The last assessment/evaluation or laboratory result obtained prior to randomization will be used to determine eligibility.

4.1. Inclusion Criteria

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

1. Subject must be 18 years of age or older
2. No prior treatment for DLBCL.
3. Criterion modified per Amendment INT-1:

   3.1 Histologically-confirmed non-GCB DLBCL

   – The verification of DLBCL will be based on central review of the local pathology report.
   – Paraffin-embedded tumor tissue (block or slides) must be sent to the central laboratory for determination of the non-GCB subtype by IHC prior to randomization (Attachment 2).
4. Stage II (not candidates for local X-ray therapy), III, or IV disease by the Ann Arbor Classification
5. At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma. The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions.
6. R-IPI score of ≥1 (Attachment 1)
7. Eastern Cooperative Oncology Group performance status grade of 0, 1, or 2 (Attachment 3)
8. Criterion modified per amendment

   8.1 Hematology values must be within the following limits prior to randomization and at baseline:

   a. Absolute neutrophil count (ANC) ≥1,000 cells/µL unless if bone marrow involvement
   b. Platelets ≥75,000 cells/µL unless if bone marrow involvement.
9. Criterion modified per amendment

   9.1 Biochemical values must be within the following limits prior to randomization and at baseline:

   a. Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN). Aspartate aminotransferase (AST) ≤3 x ULN.
   b. Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
   c. Serum creatinine ≤2 x ULN or estimated Glomerular Filtration Rate ≥40 mL/min/1.73m^2

10. LVEF within institutional normal limits, as determined by echocardiography or multiple uptake gated acquisition (MUGA) scan.
11. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For women, these restrictions apply for 12 months after the last dose of rituximab or 1 month after the last dose of study drug, whichever is later. For men, these restrictions apply for 12 months after the last dose of rituximab or 3 months after the last dose of study drug, whichever is later.
12. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
13. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands 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. Major surgery within 4 weeks of randomization
2. Known central nervous system (CNS) lymphoma
3. Known primary mediastinal lymphoma
4. Prior history of indolent lymphoma
5. Diagnosed or treated for malignancy other than DLBCL, 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
6. History of stroke or intracranial hemorrhage within 6 months prior to randomization
7. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)
8. Criterion modified per Amendment INT-1:
   8.1 Requires treatment with strong CYP3A inhibitors
9. Prior anthracycline use ≥150 mg/m^2
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

11. Criterion modified per Amendment INT-1:

    11.1 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 intravenous (IV) antibiotics (see Section 9.5). Subjects with PCR-negative HBV are permitted in the study.

12. 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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Concurrent radiation with ibrutinib is prohibited. 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 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 intrathecal CNS prophylaxis, a short ibrutinib hold (up to 3 days) should be considered based on the clinical situation of the subject, including assessment of underlying lymphoma.
- 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 arms 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 R-IPI score (1-2 vs. 3-5), region (U.S./Western Europe vs. Rest of World), and number of pre-specified treatment cycles

(6 vs. 8 cycles), then randomized in a 1:1 ratio to either Treatment Arm A (placebo+R-CHOP) or Treatment Arm B (ibrutinib+R-CHOP). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

This is a double-blind study; 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. 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.
- Personnel performing blood plasma concentration assays and analysis for pharmacokinetics.
- Unblinded sponsor safety representative and Ethics Committee for serious adverse event reporting.
- In case of an urgent safety concern, site personnel and the sponsor may be 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).

Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This 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 EFS. 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.

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

6. DOSAGE AND ADMINISTRATION

For the purposes of this study, 'study drug' refers to ibrutinib or placebo and 'study treatment' refers to ibrutinib/placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (or equivalent). The dosages for the treatment combination are described below. All dosing information must be recorded in the Dosage Administration page of the CRF. The ibrutinib treatment scheme is provided in Table 1.

6.1. Study Treatment

All subjects will receive R-CHOP (rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV [maximum total 2 mg], and prednisone [or equivalent] 100 mg orally) as the background therapy for 6 or 8 cycles per site preference (21 days/cycle). Sites may choose to administer 6 or 8 cycles of treatment based on local practice; once the number of cycles is pre-specified by the site, all subjects at individual sites are intended to receive the same number of treatment cycles (6 or 8; no individual subject adjustment permitted based on interim response) (see Table 2).

Subjects will be randomized in a 1:1 ratio to Treatment Arm A (placebo, 4 capsules orally once daily continuously + R-CHOP) or Treatment Arm B (ibrutinib 560 mg (4 x 140-mg capsules orally once daily continuously + R-CHOP). Study treatment administration begins on Cycle 1 Day 1 (within 72 hours of randomization) and ends on Day 21 of the last cycle (either 6 or 8 cycles, as pre-specified by the site), unless if the subject experiences unacceptable toxicity or disease progression. Ibrutinib or placebo will be self-administered at home.

The amount (in mg) of all study treatment, except ibrutinib, to be administered will be determined by body surface area (BSA; Attachment 4). If a subject experiences a >10% change in weight from the weight used in the previous BSA calculation, then BSA and dose should be recalculated.

6.1.1. 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 local practice at the dosages described above in Section 6.1. Refer also to the study Investigational Product Procedures Manual.

6.1.2. Ibrutinib or Placebo Administration

Subjects will be instructed to take 4 capsules of ibrutinib (for a dose of 560 mg) or placebo orally once daily, starting at Cycle 1, Day 1.

The capsules are to be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed.

Subjects should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to CYP3A inhibition. Subjects should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until seen at the site (see Section 9.3.1).

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

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

6.2. Dose Modifications and Dose Delay

Below are recommendations for the management of toxicities with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (or equivalent). However, dose modifications should be done in accordance with the respective product labels in situations that differ from dose modification guidelines specified below. Refer to the product labels and institutional guidance for complete details on adverse events for each component of R-CHOP.

Treatment-emergent adverse events of R-CHOP combination therapy predominantly comprise hematoxicities (such as neutropenia, leucopenia, thrombocytopenia, and anemia). Nonhematologic disorders such as asthenia, sensory disturbance, mucositis, alopecia, sepsis, dyspnea, back pain, hyperglycemia, hypersensitivity, and cardiac disorders have all also been reported when treatment with R-CHOP has been administered. It is not always easy to assess the role of any 1 agent in these events, and therefore; it is at the investigators discretion to decide if 1 or more agents are causal and take action as described in Sections 6.2.1 through 6.2.5.

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. If toxicity persists after a 2-week cycle delay that is related to 1 specific drug (eg, vincristine, doxorubicin, etc.), the offending drug should continue to be withheld and the new cycle should be started with the remaining drugs. If R-CHOP chemotherapy is delayed, treatment with study drug should be continued during the delay phase. Subjects who discontinue any component of R-CHOP without disease progression will continue study drug (placebo or ibrutinib) until 6 or 8 cycles (depending on the number of cycles pre-specified by each site) are completed, disease progression, or unacceptable toxicity,

whichever occurs first. If study drug is delayed or withheld, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent] may be continued. If there is a delay in the start of a new cycle of more than 3 weeks due to insufficient recovery from toxicity (with all drugs withheld), subjects will be discontinued from the study and have procedures performed as outlined in the End-of-Treatment Visit listed in the Time and Events Schedule (Table 1). However, the start of a new cycle after more than a 3-week delay (with all drugs withheld) may occur if there is clear clinical benefit and only after approval by the sponsor.

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

- Platelet count ≥75,000 cells/μL (prior platelet transfusion is allowed)
- Subjects with thrombocytopenia due to bone marrow infiltration from DLBCL 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)

6.2.1. Rituximab

There will be no dose reductions for rituximab. Rituximab should be held for any Grade 4 toxicity or for any rituximab-related, clinically significant, unmanageable Grade 3 adverse event. Rituximab should be held until the adverse event returns to baseline or resolves completely. Detailed dosing instructions for infusion reactions are provided in the product label.[42]

6.2.2. Cyclophosphamide

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 must be delayed up to 3 weeks until the above values are documented on Day 1 of the cycle. It is recommended that subjects who develop hematological toxicities thought to be causally related to cyclophosphamide have their dose adjusted on Day 1 of the subsequent cycle according to Table 6.

Table 6: 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	Initiation of G-CSF for all subsequent cycles is recommended
<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 or ANCs are not required in subjects with thrombocytopenia or neutropenia due to bone marrow infiltration from DLBCL who entered the study with platelet counts <75,000/µL or neutrophil counts <1,000 cells/µL.

6.2.3. Doxorubicin

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 as an arrhythmia may occur directly after administration and electrocardiogram 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 7:

Table 7: 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. Recommended dose reductions due to hematological toxicities are indicated in Table 6.

6.2.4. Vincristine

Dose adjustments for vincristine must follow the provided prescribing information. The vincristine dosage must be reduced if hepatic function is impaired according to Table 8:

Table 8: 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.

6.2.5. Prednisone (or Equivalent)

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.

6.2.6. Study Drug (Ibrutinib or Placebo)

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 21 consecutive days. Study drug should be discontinued permanently in the event of a toxicity lasting more than

21 days. No dose escalation of study drug (more than 4 capsules/day [ie, above 560 mg]) is allowed in this study.

The actions in Table 9 below should be taken for the following drug-related toxicities. Changes must be recorded in the Drug Accountability Forms and Dosage Administration page of the electronic CRF.

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC <0.5 x 10^9/L [ie, <500/mm^3]) for >14 days
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/mm^3]) in the presence of significant bleeding (ie, ≥Grade 2 bleeding)
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L [ie, <25,000/mm^3])
- Grade 3 or greater non-hematological toxicity

Table 9: Ibrutinib/Placebo Dose Modifications

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

Refer to Section 8.2.4 for subjects requiring the initiation of anticoagulants while receiving study drug and for instructions on dose modifications or temporary hold during concomitant administration of CYP3A inhibitors or inducers. Refer to Section 4.3 for guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

7. TREATMENT COMPLIANCE

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

7.1. Ibrutinib or Placebo Compliance

The study drug (ibrutinib/placebo) is to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. Records should be kept on the study drug accountability form provided by the sponsor or its designee. Dispensing of the study drug (ibrutinib/placebo) must be recorded in the subject's source documents. The

ibrutinib/placebo may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

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

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

7.2. R-CHOP Compliance

Background therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (or equivalent) will be provided by qualified study-site personnel and each administration will be recorded in the CRF. The site pharmacist will maintain a log of all rituximab, cyclophosphamide, doxorubicin, and vincristine vials prepared for infusion and administration. Drug supplies, if provided by the sponsor, for each subject will be inventoried and accounted for throughout the study. The infusion will be administered according to the approved prescribing information or approved institutional guidelines.

8. PRESTUDY AND CONCOMITANT THERAPY

Systemic use of the following concomitant medications will be collected in the electronic CRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, psychoanaleptics, and any anticancer therapy (including radiation). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Concomitant therapies administered at the time of, and used in the treatment of a serious adverse event, should be recorded.

8.1. Permitted Medications and Supportive Therapies

All concomitant medications for medical conditions other than DLBCL NHL are permitted other than those listed as CYP3A inhibitors, as clinically indicated. The use of growth factors is permitted in this study, but should be used according to institutional, provincial, or other guidelines (eg, American Society of Clinical Oncology) and according to the investigators site standard for use of growth factors during treatment of DLBCL with standard R-CHOP chemotherapy. All supportive therapies, other than anticancer treatment, needed for the management of subjects enrolled in this study are permitted.

8.1.1. Medications Permitted Prior to Study Treatment

8.1.1.1. Pre-treatment Steroids

Steroids are permitted prior to randomization (up to 100 mg/day prednisone or equivalent) for a maximum of 10 days. If pre-treatment steroids exceed 10 days or 100 mg/day, please consult the medical monitor for approval. If steroids are administered, they should be given after the baseline imaging assessment, baseline laboratory assessments, baseline performance status assessment, and baseline R-IPI calculation. Steroids must be recorded on the electronic CRF.

8.1.2. Medications Permitted During Treatment

The following are supportive therapies that are recommended:

- Omeprazole 20 mg/day orally or equivalent therapy for peptic ulcer
- 5HT3 antagonists or equivalent anti-emetics
- Premedication with acetaminophen (650 mg orally), diphenhydramine (50 to 100 mg IV or orally) and steroids, 30 to 60 minutes before starting each rituximab infusion, may attenuate infusion reactions
- Loperamide for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose regimen should be according to standard practice
- Bowel care is recommended to prevent constipation and should be administered per standard practice
- Platelet and RBC transfusions, and G-CSF are permitted, as necessary
- Subjects who test positive for hepatitis B surface antigen or hepatitis B core antibody at screening must have hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Hepatitis B surface antigen positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) and be treated according to local guidelines. Hepatitis B core antibody positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) or undergo regular monitoring of hepatitis B virus DNA according to local guidelines. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active hepatitis B virus infection and for signs of hepatitis during and following anti-B-cell treatment, according to local guidelines. Consultation with a hepatitis specialist is also recommended.
- Prophylactic treatment for pneumocystis carinii pneumonia is permitted according to local standards
- Central nervous system prophylaxis is allowed and recommended in accordance with local guidelines. Subjects with 1) involvement of ≥2 extranodal sites and elevated LDH, or 2) lymphomatous involvement of the bone marrow, testis, or a para-meningeal site are considered to have a high risk of developing CNS disease and should receive CNS prophylaxis according to the standard local practice. CNS prophylaxis with IV methotrexate is not permitted in this study.

8.1.2.1. Uric Acid-lowering Agents

Subjects with more than 1 of the factors listed below are considered to be at increased risk of tumor lysis syndrome and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms, including blood chemistry. Uric-acid lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric® [febuxostat] with or without rasburicase per the drug product package inserts.

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

8.2. Prohibited Medications

The following medications and supportive therapies and procedures are prohibited during the treatment phase:

- Any anticancer agent other than R-CHOP with the exception of medications that may have anticancer activity but are taken for other reasons, eg, megestrol (Megace®), Cox-2 inhibitors, and bisphosphonates
  - Anti-hormonal therapies are permitted, after discussion with the sponsor's medical monitor
- Chronic use of systemic corticosteroids above that given for R-CHOP chemotherapy. (Prednisone ≤20 mg/day or its equivalent is allowed for the treatment of adrenal insufficiency or other medical reason that is not cancer related)
- Any experimental agents other than study drug

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

8.2.1. Concomitant Use of Ibrutinib/Placebo and CYP3A Inhibitors or Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-last}}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold

treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 6.2.6).

Co-administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by approximately 10-fold. 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 5 and at http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables.[37]

8.2.2. 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. 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.

8.2.3. Concomitant Use of Ibrutinib/Placebo and QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECG) and electrolytes should be considered and, if needed, the medical monitor may be contacted.

8.2.4. 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 withheld 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.

8.2.5. Radiation Therapy

Radiation therapy must not be given concurrently with study drug. Radiation is acceptable as consolidation as per local practice (eg, for patients with baseline bulky disease, defined as having a lymph node >10 cm in the longest diameter). Note: radiation therapy can only be administered after the end of treatment efficacy assessment.

8.3. Subsequent Antilymphoma Therapies

Administration of subsequent antilymphoma therapy is not allowed until:

- Confirmed residual disease after completion of at least 6 cycles of R-CHOP,
- PD (or relapse after CR) any time during treatment as established according to the criteria described in Section 9.2.2.3, Criteria for Response Categories.

Subjects without PD and who received subsequent therapy per confirmed PET-positive or biopsy proven residual disease upon completion of at least 6 cycles of R-CHOP therapy will continue to be followed until PD. For any subsequent antilymphoma therapy, the start date, end date, and best response should be documented in the appropriate section of the electronic CRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into 3 phases: a Pretreatment (Screening) Phase, an Active Treatment Phase, and a Posttreatment Follow-up Phase. The Time and Events Schedule summarizes the frequency and timing of efficacy, PRO, pharmacokinetic, biomarker, and safety measurements applicable to this study (Table 1).

9.1.2. Pretreatment (Screening) Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. During this phase, eligibility criteria will be reviewed and a complete clinical evaluation performed as specified in the Time and Events Schedule (Table 1). The results of 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 start of study treatment 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 that assessments fulfill the study requirements and are performed within the

specified timeframe prior to randomization (Table 1). Echocardiography or multiple uptake gated acquisition (MUGA) scan is mandatory at Screening; echocardiography or MUGA may be repeated optionally at any time during the study (using same modality), as clinically indicated, either at an assessment visit or at unscheduled visit. The first FACT-Lym and EQ-5D-5L assessment will be administered prior to the first dose of study treatment. The study site staff should instruct the subject to carefully read the instructions and questions of the PRO instrument(s) prior to marking responses, that there are no right or wrong answers, and that their responses to the questionnaire will not be used to determined their study eligibility.

Investigators are required to confirm that subjects who are ≥80 years old are eligible to receive R-CHOP according to the protocol, without preplanned dose reductions.

Verification of DLBCL Diagnosis and Determination of the non-GCB Subtype

Prior to randomization, subjects with DLBCL are required to submit local pathology reports to a central laboratory for verification of diagnosis. In addition, subjects are required to submit biopsy samples (tissue block or slides) to determine DLBCL subtype (ie, non-GCB or GCB subtype) based on central IHC. One laboratory will be used to review local pathology reports for verification of DLBCL diagnosis and for determination of the non-GCB subtype based on central IHC.

Diagnosis of DLBCL will be confirmed by a local pathology report. It is important that pathology reports contain the information listed below to allow verification of the DLBCL diagnosis. At a minimum, criteria (a), (b), (e), and (f) should be included within the pathology report. (In some cases, the information in the pathology report can be supplemented with information obtained by review of the hematoxylin and eosin [H&E] slide by a central pathologist.) A report from the local laboratory must be reviewed and approved by the central pathology laboratory to verify the below criteria prior to randomization.

a. histologic documentation of entirely diffuse lymphoid architecture with no significant follicular or low grade component,
b. evidence of positive B-cell lineage,
c. presumptive evidence of monoclonality and/or aberrant neoplastic antigen expression and/or clonal immunoglobulin gene rearrangement and/or a clonal chromosomal abnormality,
d. exclusion of misclassified DLBCL,
e. documentation of a sufficient large cell component and/or increased Ki67-defined proliferative rate,
f. no pathologic evidence that DLBCL represents transformation of a pre-existing B-NHL.

A report from the local laboratory must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to randomization.

1) Diagnostic biopsy material (formalin fixed paraffin-embedded tumor tissue block or slides) will be sent to a sponsor approved central laboratory for determination of the non-GCB subtype by IHC prior to randomization. Results will be provided from the central laboratory within 4 to 7 working days from the shipment of the sample. Only subjects with central pathology laboratory IHC-confirmed non-GCB subtype of DLBCL and who fulfill all eligibility criteria will be considered eligible for participation in the study. If tissue blocks are sent, the remainder of the block will be returned after the DLBCL subtype has been confirmed.

9.1.3. Active Treatment Phase

The Active Treatment Phase will begin at randomization and will continue until discontinuation of all study treatment (ie, ibrutinib/placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [or equivalent]) due to disease progression, initiation of subsequent antilymphoma therapy, unacceptable toxicity, withdrawn, or completion of study treatment. The last measurements taken on Cycle 1 Day 1 before administration of study treatment or at Screening (whichever value was last) will be defined as the baseline values for safety assessment and treatment decision. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if they were collected more than 5 days prior to the start of study treatment (ibrutinib or placebo). These values should be consistent with the values in the inclusion and exclusion criteria (Sections 4.1 and 4.2, respectively) 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 exam (including lymphoma B-symptoms) will be conducted. 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).

All subjects will visit the study site on Day 1 of each cycle during the Active Treatment Phase. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. When all evaluations have been completed, and it has been determined that the subject may continue treatment, 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. 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 PD is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit within 30 days after the last dose of the last study treatment, and enter the Posttreatment Follow-up Phase.

End-of-Treatment Visit

Subjects who discontinue the last study treatment due to progression, adverse event, or other reasons and enter the Posttreatment Follow-up Phase should have the End-of-Treatment Visit completed before starting any subsequent antilymphoma therapy. If a subject is unable to return to the site for the End-of-Treatment Visit, the subject should be contacted to collect adverse events that occur within 30 days after the last dose of the last study treatment. Additional information on reporting adverse events may be found in Section 12.

If the subject requires subsequent antilymphoma therapy in the interim period following the last dose of study treatment and the End-of-Treatment Visit, then this visit should be completed earlier, ie, just prior to initiation of subsequent antilymphoma therapy. Refer to the Time and Events Schedule for a complete list of procedures to be performed (Table 1).

9.1.4. Posttreatment Follow-up Phase

Assessments Up to the Primary Endpoint Analysis

After the completion of the End-of-Treatment procedures, all subjects will enter a Posttreatment Follow-up Phase in accordance with the Time and Events Schedule – up to Clinical Cutoff for Primary Endpoint Analysis; Table 1). Follow-up visits, to assess disease progression, will be required if treatment is discontinued prior to PD. The interval between follow-up visits should be maintained at 16 or 24 weeks as required; if a visit occurs earlier or later than the scheduled visit date, then the next visit date should be rescheduled to maintain the required interval from the previous visit. At any visit, if there is clinical evidence or suspicion of PD, then a CT scan must be performed to document progression (See Section 9.2.2.1).

Survival follow up (physician visit or telephone contact) will be required for all subjects following PD until death, loss to follow up, consent withdrawal, or study end, whichever occurs first; and will be completed in accordance with the Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis (Table 1). The interval between Post-PD follow-up visits should be maintained at 16 weeks; if a visit occurs earlier or later than the scheduled visit date, then the next visit date should be rescheduled to maintain the required interval from the previous visit.

At the time of disease progression or if residual disease is present upon completion of at least 6 cycles, the subject is considered eligible to receive subsequent antilymphoma therapy. Subsequent antilymphoma therapy will be recorded in the electronic CRF. Subjects with residual disease who receive subsequent antilymphoma therapy will be followed until PD, clinical cutoff, or death (see the Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis, Table 1). Investigators should maintain adequate contact with the subject to obtain follow-up information on safety and survival status. Where allowed by local law, public records may be used to document death. Any new malignancy reported during the Posttreatment Follow-up Phase will be recorded in the CRF (Section 12.3.4).

The FACT-Lym will be performed until disease progression, death, or the clinical cutoff, whichever comes first. Refer to the Time and Events Schedule - Up to Clinical Cutoff for Primary Endpoint Analysis for the assessment schedule (Table 1). Following disease progression, sites should attempt to administer the EQ-5D-5L as specified in the Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis (Table 1), unless death or study end occurs first. Subjects who visit the site for the follow-up assessments should complete the EQ-5D-5L questionnaire at that time. If the EQ-5D-5L is conducted via a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the EQ-5D-5L. If the subject is unable to complete the EQ-5D-5L during the Posttreatment Follow-up Phase, the reason for not completing the questionnaire will be documented (ie, too ill, subject refused).

Assessments After the Primary Endpoint Analysis

Refer to Table 3 for the data to be collected every 24 weeks (physician visit or telephone contact). Radiologic disease evaluations may be performed as clinically indicated (at the discretion of the investigator) per local standard of care after the clinical cutoff for the primary endpoint analysis; available data may be entered into the eCRF.

9.1.5. Clinical Cutoffs

Three clinical cutoffs are planned. The first clinical cutoff will occur when approximately 270 EFS events have been observed. The second clinical cutoff will be for the final analysis of the primary endpoint EFS, and will occur approximately 30 months after the 800th subject is randomized in the study. The interim analysis and final analysis of the primary endpoint EFS will take place at these 2 clinical cutoffs, respectively. The last clinical cutoff will occur at the end of the study, when 50% of the randomized subjects have died or 5 years after the last subject is randomized or the sponsor terminates the study, whichever occurs first. Investigators will be informed when the cutoffs have occurred.

Per the original study design, the number of events required for the interim analysis is 270 EFS events. As of 12 July 2017, 230 EFS events have been reached. Due to this lower than expected EFS event rate (based on blinded data) and the short time expected between the interim and final analysis, the sponsor has omitted the first clinical cutoff for the interim analysis.

9.2. Efficacy

9.2.1. Evaluations

9.2.1.1. CT/MRI/PET Scans

During the study, disease response will be assessed using CT scans of the neck, chest, abdomen, and pelvis with IV and oral contrast as indicated and as specified in the Time and Events Schedule - Up to Clinical Cutoff for Primary Endpoint Analysis (Table 1). Subjects who are intolerant of IV CT contrast agents will have CT scans performed with oral contrast and the reason for not using IV contrast will be specified in the electronic CRF. A separate CT scan is 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 if it is of diagnostic quality. The CT scanning must be done according to the imaging requirements provided in the radiology manual to ensure that an optimized examination is done.

Evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as necessary (to be performed throughout the study using the same method of assessment per subject) may also occur at the site level. Radiological and PET scans performed prior to the database lock for the final analysis of EFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary.

Magnetic resonance imaging (MRI) may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, a scan 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.

CT scans will be performed as specified in the Time and Events Schedule – Up to Clinical Cutoff for Primary Endpoint Analysis (Table 1). A whole body PET scan will also be done at the End-of-Treatment Visit, at least 3 weeks but preferably 6 to 8 weeks after the last dose of R-CHOP. A whole body PET scan at baseline is recommended but not mandatory. Follow-up visits will be required if treatment is discontinued prior to PD. Follow-up visits, including CT scans, will be completed every 16 weeks for the first 24 months, then every 24 weeks until PD, the clinical cutoff for the primary endpoint, or up to 5 years, whichever occurs first. After that, CT may be performed as clinically indicated (at the discretion of the investigator) per local standard of care.

After disease progression, subjects will be monitored by physician visit or telephone contact to assess survival and collect subsequent antilymphoma therapy data for all subjects as specified in the Time and Events Schedules (Table 1 and Table 3). Monitoring will continue until the end of the study.

Definition of a Positive PET Scan

Assessment of PET results is based on published criteria.[26] 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 [18F]-fluorodeoxyglucose (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.

9.2.1.2. Bone Marrow Assessment

Bone marrow evaluation (biopsy + aspirate) should be done before starting treatment. Subjects with bone marrow involvement must have a repeat bone marrow evaluation at the time of CR (preferably within 30 days of the initial documentation of CR). Adequate bone marrow evaluation is required. Bone marrow evaluation must include morphological examination and also IHC, if warranted, to confirm the presence or absence of lymphoma. If bone marrow involvement can be confirmed with morphology, then IHC is not necessary if not standard practice at the site.

9.2.1.3. Fluid Aspiration at Other Sites of Disease

For sites of disease with fluid accumulation such as 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 before disease progression is diagnosed for a subject if the fluid accumulation is the only sign of disease progression.

9.2.1.4. Physical Examination

During the Screening, Active Treatment, and Posttreatment Follow-up periods (see Time and Events Schedule for procedures, Table 1), subjects should have a physical examination to evaluate the presence of palpable lymph nodes, tumor masses, or spleen and liver enlargement. Symptom-directed questions will be asked to evaluate for the presence of B-symptoms.

9.2.1.5. Patient-Reported Outcomes

Two PRO instruments, the FACT-Lym and EQ-5D-5L will be administered in this study. The FACT-Lym was originally developed to assess functional status and well-being of patients with NHL.[11] Reliability and validity have been assessed in NHL[53] and more recently construct validity has been supported in subjects with relapsed/refractory MCL.[3] The FACT-Lym consists of the Functional Assessment of Chronic Illness Therapy-General (FACT-G) and a lymphoma-specific additional concerns subscale (Lym) (Attachment 6). Responses to all items are rated on a 5-point scale ranging from 0 “not at all” to 4 “very much”. The FACT-G consists of three 7-item subscales scored 0 to 28 (physical well-being, social well-being, and functional well-being) plus one 6-item subscale (emotional well-being) scored 0 to 24. The recall period is the past 7 days. The lymphoma scale includes 15 items and scores range from 0 to 60. Two summary scores may also be calculated: the FACT-Lym total score (FACT-G plus Lym) and the FACT-Lym trial outcome index score (physical well-being + functional well-being + lymphoma). Higher scores represent better functional status and well-being for all subscales and summary scales. The subscale of most interest in this study will be the Lym subscale. Carter et al (2008)[3] and Cella et al (2005)[4] reported a minimal important change score for the Lym subscale in a relapsed/refractory MCL population range from approximately 2.9 to 5.4. Therefore, a 5-point change in the Lym subscale was selected as a conservative estimate of clinically meaningful deterioration in lymphoma symptoms. Time to complete the FACT-Lym is approximately 7 to 12 minutes.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (Attachment 7).[12] 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.[39] For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5-item questionnaire and a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). 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. The UK weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D-5L in this study. Data will be collected using electronic capture to enhance ease of collection, while flagging questions that may be missed accidently by the study subject.

After the clinical cutoff for the primary endpoint analysis, subjects will be treated according to the local standard care and available data will be entered into the eCRF. Patient-reported outcomes (EQ-5D-5L only) will be collected as specified in the Time and Events Schedule – After Clinical Cutoff for Primary Endpoint Analysis (Table 3).

9.2.2. Efficacy Criteria

9.2.2.1. Assessment of Disease Response and Progressive Disease

Efficacy assessments for the purpose of the study result analyses will be performed by the investigators according to the Revised Response Criteria for Malignant Lymphoma.[5] All efficacy assessments must continue until disease progression (even if subsequent antilymphoma therapy is started), withdrawal of consent from study participation, or clinical cutoff for the primary analysis. For all subjects with disease progression, a Study Event form accompanied with documentation of disease progression should be sent to the sponsor medical monitor within 24 hours.

9.2.2.2. Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma.[5] 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, then these other sites of measurable disease may be included as assessable disease.

9.2.2.3. Response Categories

The response categories being used to assess efficacy are based on the Revised Response Criteria for Malignant Lymphoma.[5]

Complete Response

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

1. Complete disappearance of all detectable evidence of disease and disease-related symptoms, if present before therapy.
2. All lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in the greatest transverse diameter [GTD] for nodes >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 ≤1.0 cm in the short axis after treatment. All splenic and hepatic nodules and other extranodal disease must have disappeared.
3. 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.
4. The spleen and/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.
5. If the bone marrow was involved before treatment, the infiltrate must have cleared on repeated bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). 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.).
6. No new sites of disease are detected during assessment.

Partial Response

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

1. 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.
2. No increase should be observed in the size of other nodes, liver, or spleen, meeting the criteria for PD.

3. Splenic and hepatic nodules must regress by ≥50% in the SPD or, for single nodules, in the GTD.
4. With the exception of splenic and hepatic nodules, other organs should not have any measurable disease.
5. Bone marrow assessment is not required for PR determination.
6. No new sites of disease should be observed.
7. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

Stable disease

Stable disease is defined as:

1. 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 PD.
2. The PET should be positive at, at least 1 previously involved site of disease, with no new areas of lymphoma involvement on the Posttreatment CT or PET (for the combined CT+PET assessment of stable disease).

Progressive Disease or Relapsed Disease

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

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

1. 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.
2. 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.
3. 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 PD, a lymph node with a diameter of the short axis of <1.0 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.
4. 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 PD, 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 PD. Increased FDG uptake in a previously unaffected site should only be considered PD after confirmation with other modalities.

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

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

9.2.3. Endpoints

Primary Endpoint

The primary endpoint is EFS, defined as the duration from the date of randomization to the date of disease progression, relapse from CR as assessed by the investigator, initiation of subsequent systemic antilymphoma therapy for either PET-positive or biopsy-proven residual disease upon completion of at least 6 cycles of R-CHOP therapy, or death, whichever occurs first. Refer to the Statistical Analysis Plan for further details regarding censoring rules.

Secondary Endpoint(s)

The secondary endpoints are defined as follows:

- Progression-free survival is defined as the duration from the date of randomization to the date of progression, relapse from CR, or death, whichever occurs first.
- CR rate is defined as the proportion of subjects with measurable disease who achieve CR.
- Overall survival is defined as the duration from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject will be censored at the date the subject was last known to be alive.
- Time to worsening 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.
- Pharmacokinetic parameters (eg, oral plasma clearance [CL/F], oral volume of distribution at steady state [Vss/F]) or metrics of systemic exposure (eg, AUC, minimum observed plasma concentration [C_{min}]) of ibrutinib after oral daily dosing in a subset of subjects. Parameters describing the potential relationships between ibrutinib metrics of exposure with relevant clinical, or biomarker information.
- Safety parameters of ibrutinib when combined with R-CHOP.

Exploratory Endpoints

- The mean change from baseline in EQ-5D-5L score for each postbaseline assessment.
- Biomarkers associated with resistance to ibrutinib in subjects who progress on ibrutinib treatment compared to those that remain in CR.

9.3. Pharmacokinetics

9.3.1. Evaluations

Venous blood samples of approximately 2 mL will be collected from all subjects at selected sites for measurement of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant) before dosing of study drug (ibrutinib or placebo capsules) on Day 1 of Cycles 1, 2, and 3, and postdose on Cycles 1 and 2 at 1 hour (window 45 to 75 minutes), 2 hours

(window 1.5 to 2.5 hours) and 4 hours (window 3.5 to 6 hours) after dosing of study drug (see Time and Events Schedule, Table 1). These sparse samples will be used for the development of a population-based pharmacokinetic model. It is estimated that 200 subjects on ibrutinib are needed to adequately assess this. Collection of pharmacokinetic samples will stop when this cutoff point has been reached (or earlier or later at the sponsor's discretion).

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. 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 treatment and record the exact time of study treatment 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. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.3.3. Pharmacokinetic Parameters

Population pharmacokinetic analysis of plasma concentration-time data of ibrutinib and the metabolite PCI-45227 (if deemed relevant) will be performed using nonlinear mixed-effects modeling (NONMEM), with the aim of providing estimates of pharmacokinetic parameters (eg, oral clearance) or metrics of systemic exposure (eg, AUC within the dosing interval). Model-derived plasma concentrations or metrics of exposure parameters (eg, C_{max} or AUC) may be subjected to further analyses to explore pharmacokinetic correlations between exposure and relevant clinical or biomarker information.

9.4. Companion Diagnostic and Biomarkers

9.4.1. Companion Diagnostic

A companion diagnostic device will be developed in parallel to the clinical study for determination of DLBCL subtype. The DLBCL Classification IHC [redacted] assay used to identify non-GCB and GCB subtypes is based on the Hans algorithm (2004) and utilizes a standardized IHC protocol. Subtyping will be accomplished by determination of the status of CD10, BCL6, and MUM 1. In addition, [redacted] a GEP assay for identification of the ABC DLBCL subtype that will be retrospectively determined using available clinical study FFPE tissue specimens.

9.4.2. Biomarkers

Variation in response to treatment in lymphoma may be attributable in part to disease heterogeneity. Recent studies in aggressive[43] and indolent[8] lymphoma highlight this molecular heterogeneity and identify tumor subtypes with distinct prognoses. Understanding the basic biological differences underlying disease subtypes may ultimately allow tailoring of drug

therapies for more effective treatment. Herein, we intend to identify the non-GCB subtype of DLBCL through IHC analysis of CD10, Bcl-6, and MUM1. Paraffin-embedded, formalin-fixed tumor tissue may also be analyzed for markers that may further define molecular characteristics of the non-GCB patient population or for other markers that may be implicated in drug efficacy (eg, MYD88, CARD11, NF-κB, TP53, CD79B).

Paraffin-embedded, formalin-fixed tumor tissue or cells isolated from blood collections may also be subjected to RNA analysis (eg, GEP, quantitative reverse transcription [qRT]-PCR) or somatic mutational analysis (eg, MiSeq, ExomeSEQ) from all subjects entered within this study. Comparison of IHC results may be made to transcriptomic or genomic data from matching tumor or blood to correlate molecular subtype and mutational status. Gene expression profiling and mutational analysis may also be utilized to identify other signaling pathway markers that may correlate with response to treatment (eg, CD79B, TP53, MLL2, CARD11, MYD88)[28] or other pathways/markers that may be up-regulated in the non-GCB subtype of DLBCL (eg, IL-6/STAT3).[27] Similar analyses may be carried out in a fresh tissue biopsy (ie, collected at the time of progression, if feasible) or a blood sample from subjects progressing after ibrutinib treatment. Other prognostic markers that may be analyzed include BCL-2 expression and C-MYC rearrangement.

Blood samples for biomarker evaluations will be collected from all subjects at timepoints as specified in the Time and Events Schedule (Table 1). These samples will be collected only at sites where local regulations and shipping logistics permit. Serum samples collected at the End-of-Treatment Visit and during the Posttreatment phase up to 24 months will be stored to allow for MRD assessments as necessary.

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

If it is determined at any time before study completion that additional material is needed from a formalin-fixed paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.5. Safety Evaluations

All subjects who receive treatment will undergo safety evaluations. 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. The study will be monitored by an independent DMC (details are provided in Section 11.10, Data Monitoring Committee).

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

Adverse Events

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

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 treatment. Adverse events reported after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. Progressive disease of DLBCL should not be reported as an adverse event, but instead, the clinical diagnosis that is associated with disease progression is to 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 of Special 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, Adverse Events of Special Interest, 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, then the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The local laboratory reports must be filed with the source documents.

Blood samples will be collected to assess the safety of study treatment. Required laboratory tests must be performed within 72 hours of the scheduled visit. For Day 1, Cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.

The investigator must review the local laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF.

For example, laboratory abnormalities leading to an action regarding any study treatment (dose 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 laboratory section of the electronic 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 (Table 1):

- Hematology Panel

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

- Coagulation Studies

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

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -AST
  -ALT
  -total bilirubin
  -albumin
  -uric acid
  -LDH
  -alkaline phosphatase
  -magnesium[a]

  [a] To be evaluated on Day 1 of Cycles 1 and 2, and as clinically indicated.

- Screening for hepatitis B and C will include the following evaluations: hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody. Subjects who test positive for hepatitis B surface antigen or hepatitis B core antibody must have hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Hepatitis B surface antigen positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) and be treated according to local guidelines. Hepatitis B core antibody positive subjects who are also hepatitis B DNA by PCR negative should receive prophylactic antiviral therapy (such as entecavir or tenofovir) or undergo regular monitoring of hepatitis B virus DNA according to local guidelines. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active hepatitis B virus infection and for signs of hepatitis during and following anti-B-cell treatment, according to local guidelines. Consultation with a hepatitis specialist is also recommended.
- Subjects who test positive for hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for hepatitis C after completion of the treatment for hepatitis.

- Pregnancy test (serum β-hCG or urine): for women of childbearing potential only
- Beta$_2$-microglobulin and serum immunoglobulin levels (IgG, IgM, IgA)

Vital Signs

Temperature, heart rate, and blood pressure will be recorded at Screening. Heart rate and blood pressure will also be collected on Day 1 of each cycle and at the End-of-Treatment Visit. Abnormal vital signs considered to be clinically relevant by the investigator are to be documented as adverse events.

Body Surface Area

Calculation of BSA at Cycle 1 Day 1 is required for cyclophosphamide, doxorubicin, vincristine (capped at 2 mg), and rituximab dosing. The BSA should be recalculated if a subject experiences a >10% change in weight from the weight used in the most recent BSA calculation. Weight will be collected as specified in the 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 Active Treatment phase, only a 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). An assessment of lymphoma B-symptoms (fever, night sweats and weight loss), change of status of lymph nodes, liver and spleen should also be done.

Echocardiogram or Multiple Uptake Gated Acquisition (MUGA) scans

An echocardiogram or MUGA scan is mandatory at Screening to confirm that the left ventricular ejection fraction is within institutional normal limits. The echocardiogram or MUGA may be repeated at any time during the study, as clinically indicated. When the exam is repeated, the same modality should be used.

Electrocardiogram

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).

9.6. Sample Collection and Handling

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

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

Subjects who discontinue any component of R-CHOP without disease progression will continue study drug (placebo or ibrutinib) until 6 or 8 cycles are completed (as pre-specified by each site), disease progression, or unacceptable toxicity, whichever occurs first. If study drug is discontinued, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may continue. Investigators are encouraged to keep a subject experiencing clinical benefit (ie, PR, CR, or stable disease) in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The subject experiences overt disease progression or relapse
- Unacceptable toxicity
- The subject becomes pregnant
- The subject refuses further treatment
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment

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

10.3. Withdrawal From the Study

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

- Withdrawal of consent
- The sponsor discontinues the study
- Lost to follow up

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.

11. STATISTICAL METHODS

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

All analyses will be performed based on data up to the timepoint of clinical cutoff. Long-term follow-up data will be summarized separately when the entire study has completed. Statistical inferences will be based on a 2-sided Type I rate of 0.05 unless indicated otherwise. In exploratory statistical models, main effects will be tested at the 2-sided 0.05 level, and interactions will be tested at the 0.10 level.

11.1. Analysis Populations

The analysis populations are defined as:

1. Intent-to-Treat (ITT) population: defined as all randomized subjects, who are enrolled with the non-GCB DLBCL subtype by IHC. Subjects in this population will be analyzed according to the treatment to which they are randomized.
2. ABC population: defined as all randomized subjects who are identified as having the ABC subtype as determined by GEP (retrospectively determined using available clinical study FFPE tissue specimens). Subjects in this population will be analyzed according to the treatment to which they are randomized.
3. Per-protocol population: defined as all randomized subjects who undergo at least 1 adequate postbaseline disease assessment and do not have major protocol violations including, but not limited to, the following:
    a. Did not meet all inclusion and exclusion criteria
    b. Did not receive the treatment to which they were randomized
    c. Had <75% (the cutoff values are subject to change) of study drug compliance
4. Biomarker population: defined as all randomized subjects with biomarker data collected.
5. Pharmacokinetic-evaluable population: defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 pharmacokinetic sample obtained posttreatment.
6. Safety population: defined as 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; the safety population will be used to summarize the safety data, unless otherwise specified. The biomarker population will be used to summarize the exposure and biomarker data. The pharmacokinetic-evaluable population will be used to summarize the pharmacokinetic data.

11.2. Subject Information

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

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. Percentages will be calculated by dividing the number of subjects with the characteristic of interest by the number of subjects in the analysis population and/or the evaluable population.

11.3. Sample Size Determination

This study is designed to evaluate the effect of treatment on EFS and is powered for this endpoint. DLBCL is an aggressive but potentially curable disease with 30% to 55% of patients achieving durable cure.[14] In consideration of durable cure patients in the estimation of study power and the study clinical cutoff date, the study population is differentiated as 2 subgroups based on potential curability with treatment, ie, those who could achieve durable cure (curable population; ie, those who achieve complete response and are not expected to relapse irrespective of follow-up time) and those who are not expected to achieve durable cure (non-curable population). The classic event-driven approach for obtaining a desired study power is not applicable to this study. Therefore, simulation studies were conducted in this combined population for estimation of study power with 1 planned interim analysis.

- A 1:1 randomization ratio between 2 treatment arms
- Approximately 800 subjects to be enrolled (about 400 subjects per treatment arm)
- Assuming the cure rate for the control arm (placebo+R-CHOP) is 40%, and the targeted cure rate of improvement is 10% for the active treatment arm ibrutinib+R-CHOP (ie, the cure rate for ibrutinib+R-CHOP is 50%), the median EFS is assumed to be 15 years for cured subjects
- Among those subjects not cured, a targeted hazard ratio (HR) of 0.75 is assumed. This corresponds to a 4-month increase in median EFS for the active treatment arm (ibrutinib+R-CHOP) relative to the control arm (placebo+R-CHOP), assuming the median EFS for the control arm (placebo+R-CHOP) is 12 months
- Dropout rate is 5%
- One interim analysis will be performed, when approximately 270 EFS events are available for superiority testing at a significance level of 0.002 (1-sided)

With approximately 800 subjects (about 400 subjects per treatment arm) to be randomized in approximately 27 months (30 subjects per month) and with a study follow-up period of 30 months after the 800th subject is randomized, it is anticipated that approximately 419 EFS events will be observed and the study will have at least 90% power to show the statistical significance at the overall alpha level of 0.025 (1-sided). The interim analysis will occur when approximately 270 EFS events have been observed. The clinical cutoff for the final EFS analysis is 30 months after 800th subject randomized. The alpha level for the final analysis will be calculated using the cumulative alpha spending function of power family[25] based on the actual number of events at the final analysis.

In this study, the primary endpoint analysis measures a combination of improvement in the cure rate and improvement in the EFS interval among those patients who are not cured. A statistically significant p-value indicates that the addition of ibrutinib to R-CHOP improves the clinical outcome of the experimental group when both parameters — difference in cure rate and difference in EFS of the non-cured population — are taken into account. A wide range of outcomes may result in a statistically significant difference between the groups. Table 10 presents a few examples of possible clinical outcomes and the corresponding probability that such outcomes will result in a statistically significant difference between the groups.

Table 10: Examples of Possible Study Outcomes Based on Median EFS=12 Months for Non-cured Subjects

Cure rate		EFS HR for Non-cured Subpopulation	P (success) at IA (boundary p-value = 0.002)	Cumulative P (success) at Final Analysis (either p-value <0.002 at IA or <0.024 at final analysis)
Control	Active Treated			
40%	50%	0.70	0.74	0.96
		0.75	0.61	0.92
		0.80	0.47	0.88
40%	45%	0.70	0.49	0.82
		0.75	0.33	0.70
		0.80	0.20	0.57

EFS=Event-free Survival; HR=Hazard Ration; IA=Interim Analysis; P=Probability.

As addressed in Section 11.9, the interim analysis was omitted due to the lower than expected EFS event rate.

11.3.1. Multiplicity Adjustment for ABC Subtype

The primary analysis of EFS will be performed with data from both the ITT population (by IHC) and the ABC population (by GEP) simultaneously using the method of Song and Chi (Song and Chi 2007)[46],which utilizes a 2-stage testing procedure that maintains reasonable study power while strongly controlling the familywise Type I error rate.

At Stage 1, if the p-value associated with the weighted statistic Z_1 is less than 0.04, then proceed to Stage 2 for testing both the ITT population (based on log-rank test instead of weighted testing

statistic Z_1) and the target subgroup (ABC population by GEP) at the alpha level of 0.05 separately. If the p-value for the weighted statistics Z_1 at Stage 1 is ≥0.04 and <0.2, then the ABC population will be tested at the corresponding significance level for the ABC population. The significance level for the ABC population is calculated to control the familywise error rate of 0.05 by incorporating the correlation between Z_1 and Z_2 (standardized test statistic for the ABC population by GEP). If significance is shown in the target subgroup (ABC population), then the ITT population can be re-tested at the significance level of 0.05 using a standard log-rank test. More details will be provided in the Statistical Analysis Plan.

11.4. Efficacy Analyses

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

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. The primary endpoint (EFS) will be tested using the method of Song and Chi[46] as described in Section 11.3.1. All other tests will be conducted at a 2-sided alpha level of 0.05 and 95% CI will be provided, unless stated otherwise.

11.4.1. Primary Endpoint

The primary endpoint is EFS, defined as the duration from the date of randomization to the date of disease progression, relapse from CR as assessed by the investigator, initiation of subsequent systemic antilymphoma therapy for either PET-positive or biopsy-proven residual disease upon completion of at least 6 cycles of R-CHOP therapy, or death, whichever occurs first. Event-free survival will be censored at the date of the last adequate disease assessment for subjects who do not have disease progression, subsequent systemic antilymphoma therapy, and are alive, as well as those subjects with unknown disease progression or unknown survival status at clinical cutoff. If there is no postbaseline tumor assessment and no death is observed for a subject, EFS will be censored on the date of randomization. The detailed EFS censoring rules are specified in Statistical Analysis Plan.

The stratified log rank test will be used to compare EFS distributions of the 2 treatment arms. The stratification factors to be used in the analysis are R-IPI score (1-2 vs. 3-5), region (U.S./Western Europe vs. Rest of World), and number of treatment cycles (6 vs. 8 cycles). The HR for ibrutinib+R-CHOP relative to placebo+R-CHOP and its associated 95% CI will be calculated based on the stratified Cox proportional hazards model by the stratification factors. The EFS distribution and median EFS with a 95% CI will be estimated using the Kaplan-Meier product-limit method. In case there is strong evidence of crossing hazard, other test statistics such as Rényi statistics[41] may be used. In addition, the proportional hazards cure model will be used to estimate the cure rate for each treatment arm.

11.4.2. Secondary Endpoints

11.4.2.1. Progression-free Survival

Progression-free survival is defined as the duration from the date of randomization to the date of progression, relapse, or death, whichever occurs first. Progression-free survival will be analyzed in a similar fashion as EFS.

11.4.2.2. Complete Response

Complete response rate is defined as the proportion of subjects with measurable disease who achieve CR. All randomized subjects who have a valid baseline value will be included in this analysis. Subjects with missing post-randomization data are considered non-responders. Complete response rate will be summarized using descriptive statistics for categorical data by treatment arm.

The relative risk (ibrutinib+R-CHOP vs. placebo+R-CHOP) will be reported along with the associated 95% CI. Statistical inference will be evaluated using the Cochran-Mantel-Haenszel Chi-square statistic, adjusted for the stratification factors. Logistic regression analysis will also be performed to estimate an odds ratio and its associated 95% CI between the 2 treatment arms, adjusted for the stratification factors.

11.4.2.3. Overall Survival

Overall survival is defined as the duration from the date of randomization to the date of the subject's death. Overall survival will be analyzed using the stratified log-rank test for treatment comparison. The overall survival distribution and median overall survival with its 95% CI will be estimated using the Kaplan-Meier product-limit method. The HR for ibrutinib+R-CHOP relative to placebo+R-CHOP and its associated 95% CI will be calculated based on the stratified Cox proportional hazards model by the stratification factors.

The same subgroup analysis of EFS may be performed for overall survival if the number of events within each subgroup is sufficient. In addition, the exploratory analysis, using the Cox proportional hazards model with and without the covariates, as well the exploratory analysis on the effect of subsequent antilymphoma therapy on overall survival will be performed as appropriate.

11.4.2.4. Time to Worsening on the Lym Subscale

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.

11.4.3. Other Exploratory Efficacy Endpoints

Additional exploratory efficacy endpoints are:

- Evaluate the mean change from baseline in EQ-5D-5L score for each postbaseline assessment and/or the FACT-Lym score as appropriate.
- Biomarkers associated with resistance to ibrutinib in subjects who progress on ibrutinib treatment compared to those who remain in CR.

Analyses for the exploratory efficacy endpoints will be performed using the methods specified in Section 11.4.

11.4.4. Patient-Reported Outcomes

Patient-reported outcome measures listed in Section 9.2.1.5 will be analyzed using the methods specified in Section 11.4. For individual items and sub-scale scores within the PRO measures, descriptive statistics (mean, standard deviation, median, and range) will be calculated for each timepoint, for changes from baseline at each timepoint, as well as for changes from baseline to the last value. Other exploratory analyses will be performed as appropriate.

11.5. Pharmacokinetic Analyses

Population pharmacokinetic analysis of ibrutinib plasma concentration-time data will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant structural population-based pharmacokinetic model. Available subject characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. Ibrutinib data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetics (eg, incomplete administration of the study drug; 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.

A snapshot date for pharmacokinetic samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for ibrutinib and included in the population pharmacokinetic analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population pharmacokinetic re-analysis when they become available after database lock.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

Model-derived exposure parameters may be subjected to further analyses to explore pharmacokinetic/pharmacodynamic correlations between ibrutinib exposure and relevant clinical or biomarker information. Results will be presented in a separate report.

11.7. Biomarker Analyses

Non-GCB DLBCL subjects, as assigned by IHC to exclude GCB, may be further characterized using transcriptomic (eg, GEP, qRT-PCR) and/or genomic (eg, MiSeq, ExomeSEQ) analysis. Hierarchical clustering algorithms (or similar analyses) will be utilized to evaluate gene signatures and genomic features that may affect subject response and/or effect biological characteristics of DLBCL. Genes that distinguish the DLBCL subgroup or influence drug target biology may also be compared. The effect of transcriptomic and genomic analysis on response endpoints will be tested using standard categorical tests or survival outcomes, as appropriate. Analyses will be performed across treatment arms and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (parametric or non-parametric, univariate or multivariate; for example analysis of variance or survival analysis, depending on the endpoint). Results may be presented in a separate report.

11.8. 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 by treatment arms. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the Active Treatment Phase (ie, treatment-emergent adverse events and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm. Treatment-emergent adverse events are adverse events that occur after the first dose of study treatment, and within 30 days following the last dose of study treatment; any adverse event that is considered study treatment-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens in severity or is subsequently considered study treatment-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 severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data of hematology, coagulation, and serum chemistry up to 30 days after last dose of study treatment or the End-of-Treatment 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, platelet count, total bilirubin, creatinine, alkaline phosphatase, and electrolytes (sodium, potassium). Shift tables for each cycle will be produced for selected laboratory parameters, to include hemoglobin, platelet count, WBC count, ALC, ANC, AST, ALT, LDH, total bilirubin, creatinine, alkaline phosphatase, albumin, uric acid, magnesium, and electrolytes (sodium, potassium). These 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 of the last study treatment or the End-of-Treatment Visit date, whichever is later) will also be provided. The worst toxicity grade during the study will be tabulated.

11.9. Interim Analysis

An interim analysis was planned when approximately 270 EFS events have been observed. However, as of 12 July 2017, 230 EFS events have been reached. Due to the lower than expected EFS event rate (based on blinded data) and the short time expected between the interim and final analysis (clinical cutoff for the primary analysis is 30 months after the 800th subject is randomized into the study anticipated first quarter 2018), the interim analysis will be omitted.

11.10. Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study and to evaluate the efficacy of the treatment at the time of interim analysis. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the conduct of the study. The details regarding DMC responsibilities, authorities, and procedures will be provided in a separate DMC charter.

At the interim analysis, the DMC may recommend stopping the study for efficacy, if the pre-specified stopping boundary is crossed. In addition to the planned interim analyses for efficacy, 4 safety review meetings are planned that will occur approximately 2 months after 50, 250, 450, and 650 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. Until the first safety analysis, all deaths, treatment discontinuations, and serious adverse events will be reviewed by the sponsor's responsible physician on an ongoing basis to identify safety concerns, and the DMC will be informed of any new potential signals.

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.

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.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events 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 following the last dose of study treatment. Adverse events reported after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. Resolution information after 30 days should be provided. All Grade 3 or Grade 4 adverse events considered related to study treatment must be followed until recovery to baseline or Grade ≤1. Cardiac adverse events of Grade 2 or higher will be followed until improvement to baseline or Grade ≤1. The unresolved aforementioned events will be followed for a maximum of 6 months. All adverse events of special interest as defined in Section 12.3.3 related to bleeding or resulting in bleeding complications must be followed until recovery or until there is no further improvement. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of the last study treatment, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study treatment, investigator's evaluation of its relationship to the study treatment, and the subject outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to any study treatment. 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 treatment. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

- 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 treatment 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:

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

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

12.3.3. Adverse Events of 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 event of Grade 3 or higher.*
- Any treatment-emergent serious adverse event of bleeding of any grade.
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

**All hemorrhagic adverse events requiring a transfusion of red blood cells should be reported as a Grade 3 or higher adverse events per NCI CTCAE.*

12.3.4. Other Malignancies

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

12.3.5. Pregnancy

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

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

14.1. Study Drug – Ibrutinib or Placebo

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

14.1.1. Physical Description

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

14.1.2. Packaging

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

14.1.3. Labeling

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

14.1.4. Preparation, Handling, and Storage

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

14.2. Background Therapy (R-CHOP)

Rituximab may be provided in 100 mg or 500 mg single use vials as a solution or as prescribed by the treating physician. **Cyclophosphamide**, **doxorubicin**, and **vincristine** may be provided by the sponsor as single use vials or as prescribed by the treating physician. **Prednisone** (or equivalent) may be provided by the sponsor as tablets for oral dosing or as prescribed by the treating physician.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone labels will contain information to meet the applicable regulatory requirements. Rituximab, cyclophosphamide, doxorubicin, and vincristine must be prepared in an aseptic manner according to local standards for handling cytotoxic/cytostatic drugs. Refer to the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone local prescribing information or the Site Investigational Product Procedures Manual for further instructions on preparation, handling, and storage.

14.3. Drug Accountability

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Ibrutinib Investigator's Brochure
- Ibrutinib study drug diary
- Revised Response Criteria for Malignant Lymphoma[5]
- Site Investigational Product Procedures Manual
- Imaging Manual
- Laboratory manual and supplies
- PRO questionnaires and user manuals: PRO questionnaires will include the FACT-Lym and EQ-5D-5L. The data collection format will be an electronic tablet. The format will be pre-programmed and subjects will make their responses directly on the tablet. Sample questionnaires are provided in Attachment 6 and Attachment 7.
- IWRS Manual and supplies
- Electronic data capture (eDC) Manual and electronic CRF Completion Guidelines
- Diagnosis and subtyping report form
- Subject information materials
- Informed Consent
- Study Event form (see Section 10.2)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a randomized, double blind, placebo-controlled study to compare the efficacy and safety of ibrutinib in combination with R-CHOP to R-CHOP alone in subjects with newly diagnosed DLBCL who are 18 years of age or older. All subjects will receive active treatment with R-CHOP as background therapy, which is recommended treatment by the National Comprehensive Cancer Network guidelines.[32] The study is blinded to adequately test the hypotheses that the addition of ibrutinib will prolong EFS in this subject population and provide additional clinical benefit.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted Revised Response Criteria for Malignant Lymphoma.[5] Safety assessments will occur through regular clinic visits including laboratory analyses.

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

The total blood volume to be collected is estimated at 307 to 357 mL (Attachment 8), depending on number of cycles of study drug given. The total volume of blood includes laboratory assessments associated with Screening and treatment including pharmacokinetic and biomarker samples. The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

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.

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 for molecular subtyping may be obtained separately prior to the full study ICF. 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. 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 DLBCL, to understand differences in response to drug, and to develop tests/assays

related to ibrutinib and DLBCL. 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.

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator

- A copy of the dated and signed (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 (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used. The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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

17.5. Case Report Form Completion

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

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

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

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

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first

post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRFs with the hospital or clinic records (source documents); a sample may be reviewed. 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.

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. 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 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

1. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000;403(6769):503-511.
2. Berglund M, Thunberg U, Amini RM, et al. Evaluation of immunophenotype in diffuse large B-cell lymphoma and its impact on prognosis. *Mod Pathol.* 2005;18(8):1113-1120.
3. Carter GC, Liepa A, Zimmerman AH, Morschhauser F. Validation of the Functional Assessment of Therapy – Lymphoma (FACT-LYM) in patients with relapsed/refractory mantle cell lymphoma. Poster presented at: Annual meeting of *Am Soc Hematology*; 7 December 2008; San Francisco, California.
4. Cella D, Webster K, Cashy J, et al. Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: The Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) [abstract]. *Am Soc Hematology*. 2005;106:Abstract 750.
5. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
6. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346:235-242.
7. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood.* 2010;116(12):2040-2045.
8. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004;351(21):2159-2169.
9. Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor κB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. *J Exp Med.* 2001;194(12):1861-1874.
10. Davis RE, Ngo VN, Lenz G, et al. Chronic active B cell receptor signaling in diffuse large B cell lymphoma. *Nature.* 2010;463(7277):88-92.
11. Eremenco S, Webster K, Kubkova L, Bowman, L, Cella, D. Development and multilingual validation of the FACT-Lymphoma instrument. *Quality of Life Research*. 2004;13(9):1501.
12. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16:199-208.
13. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2005;23(18):4117-4126. Epub 2005 May 2.
14. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328(14):1002-1006.
15. Flockhart DA. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed: 30 Nov 2012.
16. Friedberg JW, Fisher RI. Diffuse large B-cell lymphoma. *Hematol Oncol Clin N Am.* 2008;22:941–952.
17. Fu K, Weisenburger DD, Choi WWL, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. *J Clin Oncol.* 2008;26(28):4587-4594.
18. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.
19. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.
20. Herbrecht R, Cernohous P, Engert A, et al. Comparison of pixantrone-based regiment (CPOP R) with doxorubicin-based therapy (CHOP-R) for treatment of diffuse large b-cell lymphoma. *Ann Oncol.* 2013;00:1-6.

21. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood.* 2011;117(23):6287-6296.

22. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci.* 2010;107:13075.

23. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012. Accessed: 28 January 2013.

24. Iqbal J, Neppalli VT, Wright G, et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(6):961-968.

25. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Chapman & Hall/CRC.

26. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol*. 2007;25(5):571-578.

27. Lam LT, Wright G, Davis RE, et al. Cooperative signaling through the signal transducer and activator of transcription 3 and nuclear factor-κB pathways in subtypes of diffuse large B-cell lymphoma. *Blood.* 2008;111(7):3701-3713.

28. Lohr JG, Stojanov P, Lawrence MS, et al. Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. *PNAS.* 2012;109(10):3879-3884.

29. MabThera® (rituximab) SmPC 2013. Hertfordshire, UK. F. Roche Registration Limited. March 2013. Available at: http://www.medicines.org.uk/emc/medicine/2570. Accessed: 23 April 2013.

30. MattsonJack CancerMPact® database. Available at: http://cancermpact.mattsonjack.com/Master/Login/Login.aspx?ReturnUrl=%2fDefault.aspx. Accessed: 16 January 2013.

31. Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). *Blood.* 2003;101(11):4279-4284. Epub 2003 Feb 6.

32. National Comprehensive Cancer Network guidelines Version 1.2013. Diffuse large B-cell lymphoma. 18 December 2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed: 29 January 2013.

33. Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Blood.* 2007;109(11):4930-4935.

34. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *Chem Med Chem*. 2007;2(1):58-61.

35. Pettengell R, Johnsen HE, Lugtenburg PJ, et al. Impact of febrile neutropenia on R-CHOP chemotherapy delivery and hospitalizations among patients with diffuse large B-cell lymphoma. *Support Care Cancer.* 2012;20(3):647-652.

36. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2006;7(5):379-391.

37. Pharmacology Weekly. Available at http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables. Accessed: 31 July 2013.

38. Ponader S, Chen SS, Buggy JJ, et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. *Blood.* 2012;119(5):1182-1189. Epub 2011 Dec 16.

39. Rabin R, Oemar M, Oppe M, Janssen B, Herdman, M. EuroQol. EQ-5D-5L User Guide (Version 4.0). April 2011.

40. Récher C, Coiffier B, Haioun C, et. al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. *Lancet.* 2011;378:1858–1867.

41. Rényi, A. On the theory of order statistics. *Acta Mathematica Hungarica.* 1953;4:191-231.

42. Rituxan® (rituximab) USPI [package insert] 2013. South San Francisco, CA. Genentech, Inc. October 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf. Accessed: 23 April 2013.

43. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(25):1937-1947.

44. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol.* 2005;23(22):5027-5033.

45. Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med.* 1993;329(14):987-994.

46. Song Y, Chi GYH. A method for testing a prespecified subgroup in clinical trials. Statist. Med. 2007;26:3535-3549. Published online 1 February 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/sim.2825. Available at: http://onlinelibrary.wiley.com/doi/10.1002/sim.2825/pdf. Accessed: 2 April 2017.

47. Staudt LM, Dunleavy K, Buggy JJ, et al. The Bruton's tyrosine kinase (btk) inhibitor PCI-32765 modulates chronic active BCR signaling and induces tumor regression in relapsed/refractory ABC DLBCL. *Blood.* 2011;118:Abstract 2716.

48. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood.* 2003;102(13):4284-4289.

49. Tilly H and Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals Oncol.* 2010;21(Suppl 5):v172-v174.

50. Uptodate®. Available at: http://www.uptodate.com/contents/diffuse-large-b-cell-lymphoma-in-adults-beyond-the-basics?source=related_link. Accessed: 30 April 2013.

51. van Imhoff GW, Boerma EJG, van der Holt B, et al. Prognostic impact of germinal center-associated proteins and chromosomal breakpoints in poor-risk diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(25):4135-4142.

52. Visco C, Xu-Monette A, Miranda RN. Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. *Leukemia*. 2012;26:2103-2113.

53. Webster K, Cashy J, Cella D, et al. Measuring quality of life (QOL) in patients with non-Hodgkin's Lymphoma (NHL): The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). *Quality of Life Research*. 2005;14(9):1650.

54. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol.* 2008;26(16):2717-2724.

55. Wilson WH. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, phase 2 study. Blood (ASH Annual Meeting Abstracts) 2012;120:Abstract 686.

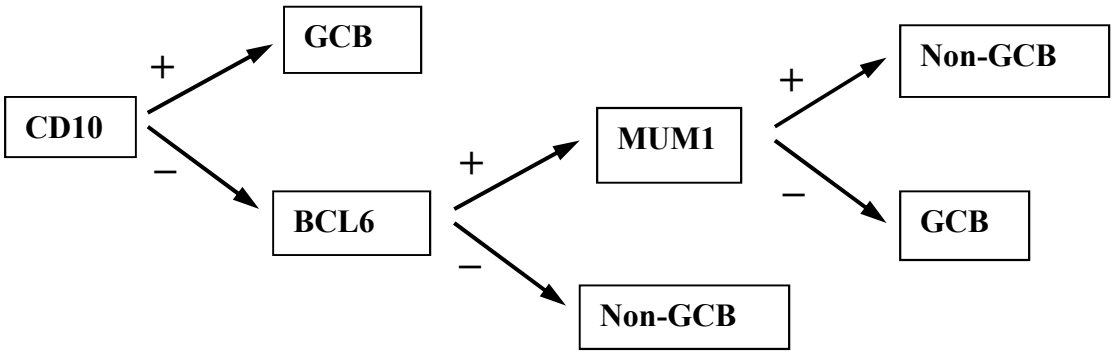
Attachment 1: Revised International Prognostic Index

The risk factors used in calculating the Revised International Prognostic Index are shown below. Give 1 point for each criterion met:

a) Age >60 years
b) Stage III or IV disease
c) Serum LDH greater than upper limit of local normal range
d) Eastern Cooperative Oncology Group performance status ≥2 (see Attachment 3)
e) More than 1 extranodal site of disease

Source: Sehn LH, Berry B, Chhanabhai M, et al. The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109(5):1857-1861.

Attachment 2: Decision Tree for Immunohistochemistry Classification of DLBCL



Source: Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.

Attachment 3: Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.

Attachment 4: Body Surface Area Calculation

BSA should be calculated using a standard nomogram. An example nomogram follows:

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Attachment 5: 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.[15,37] The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Inhibitors of CYP3A

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

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

Weak inhibitors:
cimetidine

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

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

Inducers of CYP3A

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

Attachment 6: Sample FACT-Lym (Version 4)

FACT-Lym (Version 4)

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

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

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

FACT-Lym (Version 4)

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

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

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

FACT-Lym (Version 4)

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

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

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

(English version for the UK)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

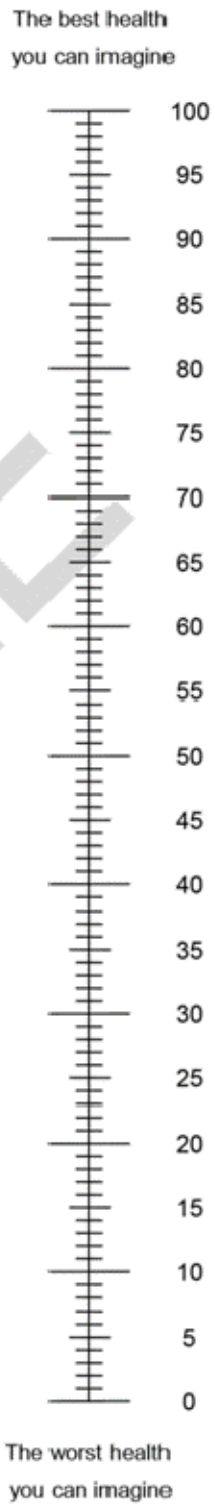
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Attachment 8: Estimated Blood Volumes for Laboratory Samples

The total blood volume for the study is approximately 307 to 357 mLs, depending on number of cycles (6 or 8) given (188 to 238 mL for safety, 18 mL for pharmacokinetics, 15 mL for serum immunoglobulin and beta$_2$-microglobulin, 12 mL for biomarkers, 70 mLs for MRD, and 4 mL for pregnancy testing [women only]).

Estimated Volume of Blood to be Collected From Each Subject (6 cycles)

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Safety (including Screening and posttreatment assessments)			
- Hematology	5	20	100
- Coagulation (INR/PT and aPTT)	5	1	5
- Serum chemistry[b]	10	8	80
Serology (hepatitis)	3	1	3
Serum β-hCG pregnancy tests	2	2	4
Pharmacokinetic samples	2	9	18
Serum IgG, IgM, IgA and beta$_2$-microglobulin	5	3	15
Biomarkers	6	2	12
Serum MRD	10	7	70
Approximate Total	48	53	307

aPTT=activated partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; HIV=human immunodeficiency virus; Ig=immunoglobulin; INR=international normalized ratio; MRD=minimal residual disease; PT=prothrombin time

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

[b] Serum chemistry includes serology (hepatitis) and serum β-hCG pregnancy tests.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Estimated Volume of Blood to be Collected From Each Subject (8 cycles)

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Safety (including Screening and posttreatment assessments)			
- Hematology	5	26	130
- Coagulation (INR/PT and aPTT)	5	1	5
- Serum chemistry[b]	10	10	100
Serology (hepatitis)	3	1	3
Serum β-hCG pregnancy tests	2	2	4
Pharmacokinetic samples	2	9	18
Serum IgG, IgM, IgA and beta$_2$-microglobulin	5	3	15
Biomarkers	6	2	12
Serum MRD	10	7	70
Approximate Total	48	61	357

aPTT=activated partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; HIV=human immunodeficiency virus; Ig=immunoglobulin; INR=international normalized ratio; MRD=minimal residual disease; PT=prothrombin time

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

[b] Serum chemistry includes serology (hepatitis) and serum β-hCG pregnancy tests.

Note: An indwelling intravenous cannula may be used for blood sample collection.

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib)

Clinical Protocol PCI-32765DBL3001 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): Jessica Vermeulen, MD, PhD

Institution: Janssen Research & Development, LLC

Signature: [redacted] Date: 17OCT2017

(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.

122

Approved, Date: 16 October 2017