PROTOCOL

Title:	A Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab in Previously Untreated Subjects with Follicular Lymphoma
Protocol Number:	PCYC-1125-CA
IND Number:	102,688
Study Drug:	Ibrutinib
Sponsor:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521
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Original Protocol Date:	24 September 2013
Amendment 1.0 Date:	12 November 2014
Amendment 1.1 Date:	11 December 2014 (Arm 2 Site Only)
Amendment 2.0 Date:	01 October 2015
Amendment 3.0 Date:	12 September 2016

CONFIDENTIALITY STATEMENT

PROTOCOL APPROVAL PAGE

Study Title: Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab in Previously Untreated Subjects with Follicular Lymphoma

Study Number: PCYC-1125-CA

Protocol Date: 24 September 2013

Amendment 1.0 Date: 12 November 2014

Amendment 1.1 Date: 11 December 2014 (Arm 2 Site Only)

Amendment 2.0 Date: 01 October 2015

Amendment 3.0 Date: 12 September 2016

I have carefully read Protocol PCYC-1125-CA entitled "Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab in Previously Untreated Subjects with Follicular Lymphoma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

14 Sep 2016

Medical Monitor's Signature Date

Jutta K. Neuenburg, MD PhD
Clinical Development, Pharmacyclics LLC

STUDY SYNOPSIS

Title:	A Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab in Previously Untreated Subjects with Follicular Lymphoma
Protocol Number:	PCYC-1125-CA
Phase:	2
Indication:	Previously untreated subjects with follicular lymphoma (FL)
Study Drug and Comparator:	Ibrutinib PO hard gelatin capsule in combination with rituximab; no comparator is used in this study.
Objectives:	**Primary** • To evaluate the efficacy of ibrutinib when combined with rituximab (determined by the overall response rate [ORR]) in previously untreated subjects with FL **Secondary** • To evaluate the efficacy of ibrutinib combined with rituximab in subjects with FL as assessed by the duration of response (DOR), progression free survival (PFS), and overall survival (OS) • To evaluate the safety and tolerability of ibrutinib combined with rituximab in previously untreated subjects with FL **Exploratory** • To determine the pharmacokinetics (PK) of ibrutinib when combined with rituximab in subjects with FL • To evaluate prognostic and predictive biomarkers relative to treatment outcomes
Study Design:	This is an open-label, Phase 2 study designed to assess the efficacy and safety of ibrutinib combined with rituximab in previously untreated subjects with FL. The study will include approximately 80 subjects with two treatment arms. **Two Treatment Arms** In Arm 1 (n = 60), subjects will receive ibrutinib 560 mg PO continuously until disease progression or unacceptable toxicity. In addition, subjects will receive rituximab 375 mg/m^2 intravenous (IV) once weekly for 4 doses for the first 4 weeks of study treatment. Subjects in Arm 1 will have imaging efficacy assessments every 12 weeks for the first 8 assessments and then every 24 weeks thereafter. In Arm 2 (n = 20), subjects will receive ibrutinib 560 mg PO continuously as a single agent for the first 8 weeks, then ibrutinib at 560 mg will continue concurrently with rituximab 375 mg/m^2 IV once weekly for 4 doses. Once treatment with rituximab is complete, subjects will continue to receive single-agent ibrutinib continuously until disease progression or unacceptable toxicity. Subjects in Arm 2 will have imaging efficacy assessments at Week 9, Week 20, and then every 12 weeks for 6 assessments after Week 20, and then every 24 weeks thereafter.

	One of the purposes of Arm 2 is to identify biomarkers that predict sensitivity or resistance to ibrutinib. Based on Phase 1 clinical data in FL it is predicted that approximately half of the subjects treated in this arm will show evidence of resistance to single-agent ibrutinib. By providing a lead-in time prior to the initiation of rituximab, pre- and post-progression biopsy samples can be collected to address markers of drug resistance. These objectives are exploratory and therefore the primary and secondary objectives related to clinical efficacy are paramount but will be analyzed separately from Arm 1 since the treatment regimen in this arm is different. The exploratory objectives are to evaluate prognostic and predictive biomarkers relative to treatment outcomes. For Arm 1, pre-treatment and post-progression tumor tissue biopsies are optional. For Arm 2, pre-treatment tumor tissue biopsy is required and post-progression tumor tissue biopsies are desired but optional. Tumor samples may be analyzed by gene expression profiling (GEP), whole exome sequencing (WES), or other methods.
Number of Subjects:	The planned sample size is 80 subjects (60 and 20 subjects in Arms 1 and 2, respectively) enrolled at multiple sites in the United States (US).
Inclusion/Exclusion Criteria:	Inclusion Criteria: Subjects must meet all of the following criteria in order to be eligible: 1. Histologically documented FL (Grade 1, 2 and 3A) 2. Not previously treated with prior anti-cancer therapy for FL 3. Stage II, III or IV disease 4. At least one measurable lesion ≥2 cm in longest diameter by CT and/or MRI scan (lesions in anatomical locations such as extremities or soft tissue lesions that are not well visualized by CT may be measured by MRI). 5. In the opinion of the investigator would benefit from therapy 6. Men and women ≥18 years of age 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 8. Life expectancy of more than 3 months, in the opinion of the investigator 9. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥2 years; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry 10. Male and female subjects who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 30 days (females) and 90 days (males) after the last dose of study drug. Female subjects who are of non-reproductive potential are exempt from this criterion

	Exclusion Criteria: Subjects who meet any of the following criteria are not eligible: 1. Medically apparent central nervous system lymphoma or leptomeningeal disease 2. FL with evidence of large cell transformation 3. Any prior history of other hematologic malignancy besides FL or myelodysplasia 4. History of other malignancies, except a) Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician. b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. c) Adequately treated carcinoma in situ without evidence of disease. 5. Major surgery within 4 weeks of first dose of study drug 6. Any life-threatening illness, medical condition, including uncontrolled diabetes mellitus (DM), or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk 7. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure (New York Heart Association [NYHA] >Class 2), unstable angina, uncontrolled hypertension, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the NYHA Functional Classification 8. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree atrioventricular (AV) block Type II, 3rd degree block, or corrected QT interval (QTc) ≥470 msec 9. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug 10. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab (RITUXAN®) 11. Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug 12. Known history of infection with human immunodeficiency virus (HIV) or history of active or chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV), or any uncontrolled active systemic infection 13. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction 14. Concurrent use of warfarin or other vitamin K antagonists

	15. Concurrent use of a strong cytochrome P450 (CYP) 3A inhibitor 16. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia 17. Any of the following laboratory abnormalities: a) Absolute neutrophil count (ANC) <1000 cells/mm^3 (1.0×10^9/L) b) Platelet count <75,000 cells/mm^3 (75×10^9/L) independent of transfusion support c) Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≥3.0 x upper limit of normal (ULN) d) Creatinine >2.0 x ULN or creatinine clearance (CrCL) <30 mL/min e) Hemoglobin <8.0 g/dL f) Bilirubin >1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) g) Prothrombin time (PT)/international normalized ratio (INR) >1.5 × ULN and partial thromboplastin time (PTT) >1.5 × ULN 18. Lactating or pregnant 19. Unwilling or unable to participate in all required study evaluations and procedures 20. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
Endpoints:	**Primary** Efficacy: • Overall response rate (Complete response [CR] + Partial Response [PR]) based on Cheson 2007 as assessed by the investigator **Secondary** Efficacy: • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) Safety: • Frequency, severity, and relatedness of treatment-emergent adverse events (AEs) • Frequency of treatment-emergent AEs requiring discontinuation of study drug or dose reductions **Pharmacokinetic (PK)** • Plasma PK of ibrutinib in combination with rituximab (Arm 1, n = 20 of a total of 60) • Plasma PK of ibrutinib alone and in combination with rituximab (Arm 2, n = 20)

	Exploratory • Change in peripheral T/B/natural killer (NK) count and profiling of immunophenotypes • Change in secreted protein levels (ie, chemokines, cytokines) • Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib (ie, gene expression profiling [GEP], whole exome sequencing [WES], etc.) • Frequency of tumor mutations (or other molecular markers) between pre- and post-treatment tissue that predict acquired resistance • Determination of minimal residual disease (MRD) in subjects with CR after ibrutinib therapy (peripheral blood [PB] and bone marrow [BM])
Safety Plan:	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify potential safety concerns. The Sponsor may schedule conference calls with the investigators to discuss study progress, obtain investigator feedback, and/or to exchange and discuss study-specific issues including AEs and SAEs.
Study Treatment:	In Arm 1 (n = 60), subjects will receive 560 mg of ibrutinib each day until disease progression or unacceptable toxicity. Rituximab 375 mg/m^2 will be given IV once weekly for 4 doses for the first 4 weeks of study treatment. In Arm 2 (n = 20), subjects will receive ibrutinib 560 mg PO continuously as a single agent for 8 weeks, then ibrutinib at 560 mg will continue concurrently with rituximab 375 mg/m^2 IV once weekly for 4 doses. Single agent ibrutinib will then continue at 560 mg until disease progression or unacceptable toxicity. Subjects may receive treatment for up to three years after the first dose of the last subject enrolled, until they enroll in an extension study, reach the time of the study closure, or discontinue from the study for any reason, whichever occurs first.
Concomitant Therapy and Clinical Practice:	**Permitted Concomitant Medications** • Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (granulocyte colony-stimulating factor [G-CSF], eg, filgrastim and pegfilgrastim) and red blood cell growth factors (erythropoietin) are permitted per institutional policy and in accordance with the American Society of Clinical Oncology (ASCO) guidelines (Smith 2006). • Transfusions may be given in accordance with institutional policy. • Short courses of corticosteroids (≤14 days) as treatment for non-cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use, arthritis, asthma, autoimmune

	cytopenia, and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. **Medications to be Used with Caution** Ibrutinib is metabolized primarily by CYP3A4. Due to the potential increase in ibrutinib exposure, concomitant use of strong CYP3A inhibitors should be avoided while the subject is receiving treatment. If use of a strong CYP3A inhibitor is indicated, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended. If ibrutinib must be administered with a strong CYP3A inhibitor, the Medical Monitor should be consulted before use, and a dose reduction of ibrutinib to 140 mg daily or temporary hold of ibrutinib should be considered. Subjects should be closely monitored for potential treatment-related toxicities. **Prohibited Concomitant Medications** • Chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy (except as stated under permitted concomitant medications) are prohibited while the subject is receiving ibrutinib. • Corticosteroids for the treatment of the underlying disease are prohibited. • Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100 mg/day of prednisone or equivalent are prohibited.
Statistical Methods:	**Analysis Methods for Arm 1** The primary analysis for all efficacy endpoints will be conducted based on the all-treated population. The all-treated population is defined as the subjects who are enrolled in the study and have received at least 1 dose of study treatment. The ORR and its 95% confidence interval (CI) will be calculated using normal approximation to the binomial distribution using Wilson's score method. If the lower bound of the CI around the ORR is greater than or equal to 53%, the primary efficacy objective is achieved. Duration of response (DOR) is defined as the interval between the date of initial documentation of a response of CR or PR, and the date of first documented evidence of progressive disease (PD), death, or date of censoring if applicable. The distribution (median, its 95% CI and Kaplan-Meier curves) of DOR will be provided using Kaplan-Meier estimates for responders in the all-treated population. Progression-free survival (PFS) will be assessed and defined as the period from the date of first dose of ibrutinib until the date of first documented evidence of PD or death, whichever occurs earlier. Overall survival (OS) is measured from the date of first dose of ibrutinib to the date of the subject's death from any cause. PFS and OS will be analyzed by the same time-to-event analysis method used for DOR.

	Analysis Methods for Arm 2 Overall Response Rate (ORR) and its 95% confidence interval will be calculated using normal approximation to the binomial distribution using Wilson's score method. Distribution of DOR, PFS and OS will be summarized using the Kaplan-Meier estimate of median and its corresponding 95% CI where the summaries are possible. **Analysis for Study Report** The analyses for the clinical study report (CSR) will occur at least 1 year after the last subject enrolled received the first dose of study drug.
Sample Size Determination:	The hypotheses test of primary endpoint analysis for Arm 1 in this study assumes an underlying response rate of 53% for first-line rituximab treatment in subjects with low grade FL (Hainsworth 2002; Freedman 2009). A sample size of approximately 60 eligible subjects is needed to exclude a 53% response rate at the 1-sided 0.025 significance level with at least 80% power, assuming a response rate of 71% is achieved.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
[^{14}C]	Carbon-14
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AV	Atrioventricular
BCR	B-cell receptor
BM	bone marrow
BR	bendamustine + rituximab
BTK	Bruton's tyrosine kinase
C	Celsius
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete remission (response)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
dL	Deciliter
DM	diabetes mellitus
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
F	Fahrenheit
FCR	fludarabine + mitoxantrone + rituximab
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEP	gene expression profiling

Abbreviation	Definition
Hr	Hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
ILD	interstitial lung disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	Intravenous
Kg	Kilogram
LDH	lactate dehydrogenase
m	Meters
MCL	mantle cell lymphoma
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	millimeter
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCYC	Pharmacyclics
PB	peripheral blood
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
pH	power of Hydrogen
PK	Pharmacokinetic
PML	progressive multifocal leukoencephalopathy

Abbreviation	Definition
PO	per os (oral)
PR	partial remission (response)
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
R-CHOP	Rituximab + cyclophosphamide + doxorubicin + vincristine sulfate + prednisone
R-CVP	Rituximab + cyclophosphamide + vincristine sulfate + prednisone
REAL	Revised European American Lymphoma
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
TEAEs	treatment-emergent adverse events
TLS	tumor lysis syndrome
t ½	half-life
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
WES	whole exome sequencing
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia

1. BACKGROUND

For more detailed and comprehensive background information, please refer to the current ibrutinib Investigator's Brochure (IB).

1.1 Follicular Lymphoma

Follicular lymphoma (FL) is one of the most common types of Non-Hodgkin's Lymphoma (NHL) accounting for approximately 22% of cases (NHL Classification Project 1997), and for about 70% of indolent lymphomas (NHL Cyber family web site). Follicular lymphoma is characterized by an indolent clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients (Relander 2010). The overall incidence of B-cell lymphoid neoplasms in the United States (US) is estimated at 26.13/100,000 person years (Morton 2006), with FL accounting for 3.18 new cases per 100,000 persons each year in the US and 5 to 7 new cases per 100,000 persons each year in the European Union (EU) (Dreyling 2011). The neoplastic lymphocytes in FL express pan-B markers CD19, CD20, CD22, and CD79a; as well as antigens of the germinal center (including CD10 and Bcl-6). Histologically, the follicular form of NHL is composed mainly of centrocytes with an admixture of centroblasts. Grading is based on the number of large transformed cells in 10 malignant follicles viewed at high power (Martinez 2007). Follicular lymphoma is generally subdivided into 3 grades (NHL Classification Project 2007). However, Grade 3 is often further divided into 2 subgroups, 3a and 3b; with 3b considered more aggressive (Hans 2003). Treatment depends on the stage of the disease, symptoms, patient age, and comorbidities.

The best time to initiate therapy is a decision of the individual oncologist managing the individual patient. Current guidelines (eg, National Comprehensive Cancer Network [NCCN]) are somewhat flexible; therapies and therapy start times are variable. Some treating oncologists especially for patients in earlier stages of disease prefer a watch-and-wait approach in an attempt to manage disease symptoms and treatment toxicities (Colombat 2001; Young 1988). Since FL is slow growing, it may take years for the disease to progress, during which time treatment may not be necessary. Depending on a patient's symptoms, early treatment may not always improve overall survival, especially if the disease is not affecting their organs (Colombat 2001).

Patients with Stage III or IV FL who have involvement of multiple lymph node regions, involvement of one or more organs or tissues outside the lymphatic system, and systemic symptoms, are candidates for immediate therapy. When the decision to treat has been made, initial therapy may include rituximab as a single agent. Two single-arm studies have been published that form the basis for the NCCN guidelines for rituximab in the first line setting. In the first study with 49 patients with low tumor burden where rituximab was given for a total of 4 weekly doses, patients were eligible for inclusion if they had follicular NHL according to the Revised European American Lymphoma (REAL) classification (Harris 1994); disease stage was II to IV according to Ann-Arbor classification, and the presence of at least one measurable disease site was required (Colombat 2001). The overall response rate (ORR) was 73% and the

time to progression was 50% after the first year (Colombat 2001). In the second study, 60 patients were treated with 4 weekly doses of rituximab followed by maintenance therapy at 6-month intervals until progression (Hainsworth 2002). Inclusion criteria included biopsy-proven indolent B-cell NHL as defined by the REAL classification; disease stage was II to IV or disease Stage I or II if relapsed or progressed after radiation therapy (Hainsworth 2002). The ORR was 47% and long-term follow data had a progression-free survival (PFS) of 34 months (Hainsworth 2002).

A third larger study in 349 treatment-naïve patients treated with 4 weekly courses of rituximab showed an ORR of 59% (Freedman 2009). This study included patients with histologically confirmed CD20+ FL World Health Organization (WHO) Grade 1 to 3 who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Freedman 2009). The long-term outcome of this study is hard to interpret due to further randomization to an experimental regimen.

In patients with large tumor burdens, rituximab may be combined with 1 or more cytotoxic drugs. Alkylating agents such as cyclophosphamide or bendamustine, in combination with rituximab, constitute the mainstay of combination therapy. The most commonly used alkylator-based regimens include BR (bendamustine and rituximab), R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) (Lymphoma Research Foundation 2011). Response rates in excess of 85% are observed with many different combinations in the first-line setting (Peterson 2003; Hiddeman 2005; Czuczman 2005; Rummel 2005); however these treatments are associated with significantly more toxicity than single-agent rituximab.

Due to the toxicity seen with standard combination treatment regimens in patients who are elderly, and for patients that have moderate tumor burdens and non-life threatening disease, an initial chemotherapy-free regimen such as rituximab and ibrutinib may be an attractive treatment option if found to be well tolerated and have significant anti-tumor activity.

1.2 Ibrutinib Background

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies. Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL with a deletion of the short arm of chromosome 17 (del17p), and patients

with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the BCR, which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that 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 postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib IB.

1.3 Summary of Nonclinical Data

1.3.1 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell

receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011). Ibrutinib also inhibited adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a; Chang 2013b).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.

1.3.2 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and in the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study, ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC [area under the curve]) in patients administered the dose of 560 mg daily, respectively.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the IB.

1.3.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.4 Summary of Clinical Studies

Ibrutinib is under late-stage development as an orally administered anticancer agent for patients with B-cell malignancies. As of the 06 April 2014 data cutoff date, there are 26 ongoing and 9 completed company-sponsored clinical trials investigating the safety, efficacy and pharmacokinetics (PK) of ibrutinib in humans as a single agent and in combination with chemotherapy and immunotherapy. Ongoing and completed company-sponsored clinical studies of ibrutinib are summarized in the current version of the IB.

1.4.1 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of a human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for subjects with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance) in this study. There is no data in patients with severe renal impairment or subjects on dialysis. Following single dose administration, the AUC 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. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

1.4.2 Summary of Clinical Safety

For more comprehensive safety information please refer to the current version of the IB.

1.4.2.1 Monotherapy Studies

Pooled safety data for a total of 1318 subjects treated with ibrutinib monotherapy from 13 studies that have completed primary analysis or final analysis included in the CSR as of the 31 May 2016 cutoff date for the current Investigator's Brochure update in B-cell malignancies are summarized below. Data for subjects in Study 1112 and in Study MCL3001 who crossed over from the comparator arm to ibrutinib treatment after progression are not included.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs ≥15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhoea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of IB; [b] Source is Table 8 of IB; [c] Source is Table 9 of IB.

1.4.2.2 Combination Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Data from subjects in Study CLL3001 who crossed over from the comparator arm to ibrutinib treatment after progression are not included.

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs ≥20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anaemia	Anaemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhoea	

[a] Source is Table 10 of IB; [b] Source is Table 12 of IB; [c] Source is Table 13 of IB.

1.4.3 Risks

1.4.3.1 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. 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. See Section 6.1.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.2 for guidance on ibrutinib management with surgeries or procedures.

1.4.3.2 Lymphocytosis and Leukostasis

Leukostasis

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

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating lymphocytes e.g. >400,000/μL) 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 and typically resolves within a median of

8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. Lymphocytosis was not observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib.

1.4.3.3 Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.1).

1.4.3.4 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

1.4.3.5 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4.1).

1.4.3.6 Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) 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.

1.4.3.7 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.4.1).

1.4.3.8 Non-melanoma Skin Cancer

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

1.4.3.9 Rash

Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens - Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, angioedema have been reported.

1.4.3.10 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.4.3.11 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.5 Justification of Study Design and Dose Rationale

This is an open-label, Phase 2 study designed to assess the safety and efficacy of ibrutinib and rituximab in subjects with previously untreated FL. Rituximab, given either as a single agent or in combination, is currently a recommended therapy for previously untreated FL. All subjects will receive ibrutinib and rituximab; the study will include two treatment arms with 60 subjects in the main study arm and 20 subjects in the exploratory study arm. For the 60 subjects in Arm 1, the study will determine clinically meaningful efficacy for the combination of ibrutinib and rituximab in untreated FL subjects. Assuming an ORR of 53% for single-agent rituximab, a response rate of 71% for the combination of ibrutinib and rituximab implies an 18% improvement in ORR over rituximab alone. With a sample size of 60, an 18% change in ORR will be detected with 81% power at 1-sided significance level 0.025 (or 2-sided significance level 0.05).

The proposed dose for rituximab is 375 mg/m^2 intravenous (IV) administered once weekly for 4 weeks. This dose was given in two single-arm published studies that form the basis for the

NCCN guidelines for rituximab in the first-line setting (Colombat 2001; Hainsworth 2002) and has been used in relapsed/refractory FL (McLaughlin 1998).

The proposed dose for ibrutinib is 560 mg per day (4 x 140-mg capsules) administered once daily without interruption. In the Phase 1 study (PCYC-04753), the 560 mg dose administered once daily appeared safe and favorable responses were seen in subjects with NHL as outlined above.

Study PCYC-04753 was a first-in-human, Phase 1, dose-escalating study of ibrutinib in subjects with recurrent B-cell lymphoma including NHL, CLL, FL, MCL, and WM. Five sequential cohorts of subjects received ibrutinib from 1.25 to 12.5 mg/kg/day for 28 days of a 35-day cycle and 2 additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg/day or a 560-mg fixed dose.

Sixty-six (66) subjects were enrolled including 16 subjects with FL. Of the 16 subjects with FL, 11 (68.8%) were evaluable for response. The ORR for these 11 subjects was 45.5%, with 3 complete responses (CR, 27.3%) and 2 partial responses (PR, 18.2%) and median PFS was 13.4 months. Five (45.5%) of the six remaining subjects had stable disease (SD).

These data imply relevant anti-tumor activity in the indolent lymphoma patient population. In Study PCYC-04753, ibrutinib was well tolerated across a broad range of doses (1.25 through 12.5 mg/kg/day) both when given intermittently and continuously on a 35-day cycle to subjects with a variety of lymphoid malignancies. The most common AEs (>20% of subjects) in this population were diarrhea, fatigue, cough, nausea, headache, and pyrexia. AEs were generally mild to moderate (Grade 1 or 2) and readily managed or reversible. There was no apparent relationship between the incidences or severity of AEs and dose or schedule of ibrutinib. In addition, the maximum tolerated dose of ibrutinib was not reached. Pharmacodynamic studies revealed complete BTK active-site occupancy in PBMCs at doses of 2.5 mg/kg and above, including the 560 mg continuous dosing cohort. In addition, because of an expected tissue-to-plasma concentration ratio of 50% in more distant compartments, such as blood-forming organs (bone marrow, spleen, and lymph node) and lymphoid tumor tissue (based on ratio data in the range of 0.44 to 0.67 observed in rat), it is reasonable to expect full BTK occupancy in these tissues at doses of 5 mg/kg and above.

Taken together, these data support the proposed doses for the combination of rituximab and ibrutinib. If the combination is effective and well tolerated, further investigation in the treatment-naïve FL population will be warranted.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of ibrutinib when combined with rituximab (determined by the ORR) in previously untreated subjects with FL.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of ibrutinib combined with rituximab in subjects with FL as assessed by the duration of response (DOR), PFS, and overall survival (OS)
- To evaluate the safety and tolerability of ibrutinib combined with rituximab in previously untreated subjects with FL

2.3 Exploratory Objective

The exploratory objectives are:

- To determine the pharmacokinetics (PK) of ibrutinib when combined with rituximab in subjects with FL
- To evaluate prognostic and predictive biomarkers relative to treatment outcomes

3. STUDY DESIGN

3.1 Description of Study

This is an open-label, Phase 2 study designed to assess the efficacy and safety of ibrutinib combined with rituximab in previously untreated subjects with FL. The study will include approximately 80 subjects with two treatment arms.

In Arm 1 (n=60), subjects will receive ibrutinib 560 mg per oral (PO) continuously until disease progression or unacceptable toxicity. In addition, subjects will receive rituximab 375 mg/m^2 IV once weekly for 4 doses for the first 4 weeks of study treatment. Subjects in Arm 1 will have imaging efficacy assessments every 12 weeks for the first 8 assessments and then every 24 weeks thereafter.

In Arm 2 (n=20), subjects will receive ibrutinib 560 mg PO continuously as a single agent for the first 8 weeks, then ibrutinib at 560 mg will continue concurrently with rituximab 375 mg/m^2 IV once weekly for 4 doses. Once treatment with rituximab is complete, subjects will continue to receive single-agent ibrutinib continuously until disease progression or unacceptable toxicity. Subjects in Arm 2 will have imaging efficacy assessments at Week 9, Week 20 and then every 12 weeks for 6 assessments after Week 20, and then every 24 weeks thereafter. Subjects who progress prior to starting rituximab will be discontinued from the study. Rituximab will not be administered prior to the protocol-specified administration.

One of the purposes of Arm 2 is to identify biomarkers that predict sensitivity or resistance to ibrutinib. Based on Phase 1 clinical data in FL it is predicted that approximately half of the subjects treated in this arm will show evidence of resistance to single-agent ibrutinib. By providing a lead-in time prior to the initiation of rituximab, pre- and post-progression biopsy

samples can be collected to address markers of drug resistance. These objectives are exploratory and therefore the primary and secondary objectives related to clinical efficacy are paramount but will be analyzed separately from Arm 1 since the treatment regimen in this arm is different.

For Arm 1, pre-treatment and post-progression tumor tissue biopsies are optional. For Arm 2, pre-treatment tumor tissue biopsy is required and post-progression tumor tissue biopsies are desired but optional. Tumor samples may be analyzed by gene expression profiling (GEP), whole exome sequencing (WES), or other methods.

Subjects may receive treatment for up to three years after the first dose of the last subject enrolled, until they enroll in an extension study, reach the time of the study closure, or discontinue from the study for any reason, whichever occurs first. Reasons for treatment discontinuation are outlined in Section 8.2.

3.2 Endpoints

3.2.1 Primary Endpoint

Overall response rate (Complete response [CR] + Partial Response [PR]) based on Cheson 2007 as assessed by the investigator

3.2.2 Secondary Endpoints

- Efficacy:
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
- Safety:
  - Frequency, severity, and relatedness of AEs
  - Frequency of AEs requiring discontinuation of study drug or dose reductions

3.2.3 Pharmacokinetic (PK) Endpoints

- Plasma PK of ibrutinib in combination with rituximab (Arm 1, n=20 of a total of 60)
- Plasma PK of ibrutinib alone and in combination with rituximab (Arm 2, n=20)

3.2.4 Exploratory Endpoints

The exploratory endpoints are as follows:

- Change in peripheral T/B/natural killer (NK) count and profiling of immunophenotypes
- Change in secreted protein levels (ie, chemokines, cytokines)

- Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib (ie, GEP, WES, etc.)
- Frequency of tumor mutations (or other molecular markers) between pre- and post-treatment tissue that are associated with acquired resistance
- Determination of minimal residual disease (MRD) in subjects with CR after study treatment (peripheral blood [PB] and bone marrow [BM])

3.3 Safety Plan

This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Treatment-emergent AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Enrolled subjects will also be evaluated clinically including vital signs and standard laboratory test assessment. The Sponsor may schedule conference calls with the investigators to discuss study progress, obtain investigator feedback and exchange, and discuss study-specific issues including AEs and SAEs and discontinuations of study drug.

3.4 Statement of Compliance

This study will be conducted in compliance with this protocol, principles of International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

4. SUBJECT SELECTION

4.1 Number of Subjects

The planned sample size in Arm 1 (main study arm) is 60 subjects enrolled at multiple sites in the US. Other regions may be considered based on overall enrollment.

The planned sample size in Arm 2 (exploratory study arm) is 20 subjects enrolled at a single site in the US.

4.2 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet all of the following criteria:

1. Histologically documented FL (Grade 1, 2 and 3A)
2. Not previously treated with anti-cancer therapy for FL
3. Stage II, III or IV disease
4. At least one measurable lesion ≥2 cm in longest diameter by CT and/or MRI scan (lesions in anatomical locations such as extremities or soft tissue lesions that are not well visualized by CT may be measured by MRI)

5. In the opinion of the investigator would benefit from therapy
6. Men and women ≥18 years of age
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
8. Life expectancy of more than 3 months, in the opinion of the investigator
9. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥2 years; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
10. Male and female subjects who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 30 days (females) and 90 days (males) after the last dose of study drug. Female subjects who are of non-reproductive potential are exempt from this criterion.

4.3 Exclusion Criteria

Subjects will be ineligible for this study if they meet any of the following criteria:

1. Medically apparent central nervous system lymphoma or leptomeningeal disease
2. FL with evidence of large cell transformation
3. Any prior history of other hematologic malignancy besides FL or myelodysplasia
4. History of other malignancies, except
    a. Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease
5. Major surgery within 4 weeks of first dose of study drug
6. Any life-threatening illness, medical condition, including uncontrolled diabetes mellitus (DM), or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk
7. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure (New York Heart Association [NYHA] >Class 2), unstable angina, uncontrolled hypertension, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the NYHA Association Functional Classification
8. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree atrioventricular (AV) block Type II, 3rd degree block, or QTc ≥470 msec

9. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug
10. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab (RITUXAN®)
11. Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug
12. Known history of infection with human immunodeficiency virus (HIV) or history of active or chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV), or any uncontrolled active systemic infection
13. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction
14. Concurrent use of warfarin or other vitamin K antagonists
15. Concurrent use of a strong cytochrome P450 (CYP) 3A inhibitor
16. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia
17. Any of the following laboratory abnormalities:
    a. Absolute neutrophil count (ANC) < 1000 cells/mm^3 (1.0 x 10^9/L)
    b. Platelet count < 75,000 cells/mm^3 (75 x 10^9/L) independent of transfusion support
    c. Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3.0 x upper limit of normal (ULN)
    d. Creatinine > 2.0 x ULN or creatinine clearance (CrCL) < 30 mL/min
    e. Hemoglobin < 8.0 g/dL
    f. Bilirubin > 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
    g. Prothrombin time (PT)/international normalized ratio (INR) > 1.5 × ULN and partial thromboplastin time (PTT) > 1.5 × ULN
18. Lactating or pregnant
19. Unwilling or unable to participate in all required study evaluations and procedures
20. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)

5. TREATMENT OF SUBJECTS

5.1 Enrollment and Blinding

This is an open-label, Phase 2 study with two treatment arms. Subjects will not be blinded to study drug nor will they be randomized. Enrolled subjects will receive open-label ibrutinib capsules in combination with rituximab.

5.2 Formulation, Packaging and Storage

5.2.1 Ibrutinib

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

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Please refer to the pharmacy manual for additional guidance on study drug preparation, handling and storage.

5.2.2 Rituximab

Rituximab (RITUXAN®) is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL. In addition, rituximab, given either as a single agent or in combination, is currently a recommended therapy for previously untreated FL per the NCCN guidelines. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Rituximab vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F). Vials should be protected from light.

Rituximab prescribing information can be found at
http://www.gene.com/download/pdf/rituxan_prescribing.pdf

5.3 Dosage and Administration

Below are specific administration instructions for the agents used within this study. Subjects with an increased risk of TLS should be carefully monitored and treated per institutional standards, as appropriate.

5.3.1 Ibrutinib

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. On the days when subjects receive both ibrutinib and rituximab, ibrutinib will be administered first and rituximab will be infused within 30 min of the ibrutinib dose. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 4).

Ibrutinib dosing is continuous (without interruption) throughout the treatment phase. If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up missed doses of ibrutinib should be taken.

If rituximab dosing is delayed for toxicity that does not require ibrutinib to be held for toxicity, dosing should continue at the investigator's discretion. If a rituximab infusion is delayed due to scheduling delays, ibrutinib dosing should continue.

Ibrutinib will be dispensed to subjects in bottles. All doses of ibrutinib taken in the clinic should be taken from the bottle dispensed to the subject. Unused ibrutinib capsules dispensed during previous visits must be returned to the site and drug accountability records (Section 11.8) must be updated. Returned capsules must not be re-dispensed to anyone. Subjects should return all used bottles to the site when they receive new study drug. For the purpose of drug accountability, empty bottles and returned capsules should be kept at the site until after the review of the site monitor if allowed by local institution policy.

Investigators are prohibited from supplying ibrutinib capsules to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as Subinvestigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that subjects receive ibrutinib capsules only from personnel who fully understand the procedures for administering the drug.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 8.2.

Dose modifications for toxicity are outlined in Section 5.4.

5.3.2 Rituximab

Rituximab is given at 375 mg/m^2 IV infusion once weekly for 4 doses.

Since rituximab, given either as a single agent or in combination, is currently a recommended therapy for subjects with previously untreated FL per the NCCN guidelines, the costs for administering rituximab are expected to be covered by the individual subject's insurance.

Per Prescribing Information:

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs.

If hypersensitivity or infusion reactions do not occur, the infusion rate may be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of subject symptoms.

Subsequent Infusions: If the subject tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the subject did not tolerate the first infusion well, follow the guidelines for the first infusion.

Some individual subjects may require close monitoring during the first and all subsequent infusions, eg subjects who have pre-existing cardiac or pulmonary conditions, prior clinically significant cardiopulmonary AEs or high numbers of circulating malignant cells ($\geq$25,000/mm^3) with or without evidence of high tumor burden.

5.4 Dose Reduction, Delay and Discontinuation

5.4.1 Ibrutinib

The ibrutinib dose should be held for any unmanageable, potentially ibrutinib-related toxicity that is consistent with the rules outlined in this section.

Please see Section 10.2.4 for reporting of major hemorrhage and intracranial hemorrhage (Section 10.2.4.1).

The action in Table 1 should be taken for the following ibrutinib-related toxicities:

- Grade 4 ANC (<500/µL) for more than 7 days. The use of neutrophil growth factors is permitted per American Society of Clinical Oncology (ASCO) guidelines (Smith 2006) and must be recorded in the electronic case report form (eCRF).
- Grade 3 thrombocytopenia (<50,000/µL) for subjects with normal platelet count at baseline; or for subjects with baseline thrombocytopenia, a platelet decrease of 50% to 74% from baseline in the presence of >Grade 2 bleeding
- Grade 4 thrombocytopenia (<25,000/µL) for subjects with normal platelet count at baseline; or for subjects with baseline thrombocytopenia, a platelet decrease of ≥75% from baseline or <20,000/µL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy

- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.1.2.4).

Table 1: Dose Modification for Ibrutinib Toxicity

Occurrence	Action to be Taken
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (420 mg per day)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (280 mg per day)
Fourth	Discontinue ibrutinib

At the investigator's discretion, the dose of ibrutinib may be re-escalated after a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Study treatment should be discontinued in the event of a toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

In the event that the investigator feels deviation from the recommendations above is required, please consult the Medical Monitor to discuss for approval.

Please see Section 6.1.2.1 for guidelines for management of ibrutinib in subjects who require treatment with a strong CYP3A inhibitor.

Dose modifications of ibrutinib must be recorded in the eCRF.

5.4.1.1 Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 6).

5.4.2 Rituximab

At the investigator's discretion, the rituximab dose should be held for any unmanageable, potentially rituximab-related toxicity that is consistent with the rules outlined in this section.

A missed dose of rituximab on the weekly schedule for any reason will not be made up (the visit window for this visit is ± 2 days). Upon recovery as outlined in Section 5.4, subjects should resume the protocol-specified treatment schedule as soon as possible.

The dose of rituximab should be modified according to the dose modification guidelines in Table 2 if any Grade 4 or unmanageable Grade 3 non-hematologic toxicity attributed to rituximab occurs.

Table 2: Dose Modification for Rituximab Toxicity

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

Dose modifications of rituximab must be recorded in the eCRF.

5.5 Overdose Instructions

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 10.2 for further information regarding AE reporting.

5.6 Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 8.2.

Subjects who withdraw for any reason other than those specified in Section 8.2 will not be replaced. A Safety Follow-up visit (Section 7.1.3.1) is required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1 Concomitant Medications

6.1.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (granulocyte colony-stimulating factor [G-CSF], eg, filgrastim and pegfilgrastim) and red blood cell growth factors (erythropoietin) are permitted per institutional policy and in accordance with ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses of corticosteroids (≤14 days) as treatment for non-cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use, arthritis, asthma, autoimmune cytopenia, and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

6.1.2 Medications to be Used with Caution

6.1.2.1 CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A4 (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, the Medical Monitor should be consulted before use, reduce ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1).

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

For subjects who must take strong or moderate CYP3A inhibitors while on treatment with ibrutinib, additional PK blood samples during concomitant use of ibrutinib with strong or moderate CYP3A inhibitors will be requested for ibrutinib exposure confirmation (see Section 7.3.21).

A list of common CYP3A inhibitors and inducers is provided in Appendix 4; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

6.1.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.

6.1.2.3 QT Prolongation

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

6.1.2.4 Antiplatelet Agents and Anticoagulant

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries, see Section 6.2.

6.1.3 Prohibited Concomitant Medications

Chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy (except as stated under the permitted concomitant medications) are prohibited while the subject is receiving ibrutinib.

Corticosteroids for the treatment of the underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100 mg/day of prednisone or equivalent are prohibited.

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

6.2 Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. STUDY PROCEDURES

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments for Arms 1 and 2 are provided in Appendix 1 and Appendix 2.

7.1 Visit Procedures

For a full explanation of all procedures, please refer to Section 7.3.

7.1.1 Screening

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window, with the exception of tumor tissue biopsy.

The following procedures will be performed during Screening:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- B-symptom collection
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [≥1 minute apart])
- Review of prior medications (including over-the-counter drugs, vitamins and herbs)

- Imaging by CT/MRI
- Imaging by positron emission tomography (PET)
- Bone marrow aspirate and biopsy (including MRD)
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Coagulation (PT, PTT, INR)
  - Serum pregnancy test (for women of childbearing potential only)
  - Hepatitis serologies
  - Urinalysis
- Research laboratory blood samples for:
  - Biomarkers
- Tumor tissue biopsy (optional for Arm 1 and required for Arm 2) – may be archival

7.1.2 Treatment Phase

7.1.2.1 Arm 1

7.1.2.1.1 Week 1/Day 1

Subjects who are deemed eligible will return to the clinic on Week 1, Day 1. The following procedures will be performed:

Pre-Dose

- Confirmation of eligibility
- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - T/B/NK cell counts
  - Biomarkers
- Review of concomitant medications

Dosing and Post-Dose

- Dispense ibrutinib
- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- Biomarkers (4 hrs [±30 mins] after administration of ibrutinib)
- Review of AEs and concomitant medications

7.1.2.1.2 Week 2/Day 8

The following procedures will be performed on Week 2, Day 8 (±2 days):

Pre-Dose

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- Review of AEs and concomitant medications

7.1.2.1.3 Week 3/Day 15

The following procedures will be performed on Week 3, Day 15:

Pre-Dose

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry

- Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - PK
  - T/B/NK cell counts
  - Biomarkers
- Review of AEs and concomitant medications

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- PK (see Section 7.3.20 for timepoints)
- Biomarkers (4 hrs [±30 mins] after administration of ibrutinib)
- Review of AEs and concomitant medications

7.1.2.1.4 Week 4/Day 22

The following procedures will be performed on Week 4, Day 22 (±2 days):

Pre-Dose

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- Review of AEs and concomitant medications

7.1.2.1.5 Week 5/Day 29

The following procedures will be performed on Week 5, Day 29 (±2 days):

- Complete physical exam
- ECOG Performance Status

- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications
- Drug Accountability
- Dispense ibrutinib

7.1.2.1.6 Every 4 Weeks from Week 9 until Treatment Termination

Visits will be performed every 4 weeks (±2 days) starting at Week 9 until completion of the Week 49 Visit and then every 12 weeks (±2 days) thereafter. All visits will be scheduled in relation to Day 1. Visit windows are relative to the Day 1 visit date. The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 12 weeks from Day 1 [or at the closest associated visit] for women of childbearing potential only)
- Weeks 9 and 13 only - Research laboratory blood samples collected for:
  - T/B/NK cell counts
  - Biomarkers
- Review of AEs and concomitant medications
- Drug accountability
- Dispense ibrutinib

7.1.2.2 Arm 2

7.1.2.2.1 Week 1/Day 1

Subjects who are deemed eligible will return to the clinic on Week 1, Day 1. The following procedures will be performed:

Pre-Dose

- Confirmation of eligibility
- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - T/B/NK cell counts
  - Biomarkers
- Review of concomitant medications

Dosing and Post-Dose

- Dispense ibrutinib
- In-clinic administration of ibrutinib
- Biomarkers (4 hrs [±30 mins] after administration of ibrutinib)
- Review of AEs and concomitant medications

7.1.2.2.2 Week 3/Day 15

The following procedures will be performed on Week 3, Day 15:

Pre-Dose

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - PK
  - T/B/NK cell counts
  - Biomarkers
- Review of AEs and concomitant medications

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- PK (See Section 7.3.20 for timepoints)
- Biomarkers (4 hrs [±30 mins] after administration of ibrutinib)
- Review of AEs and concomitant medications

7.1.2.2.3 Week 5/Day 29

The following procedures will be performed on Week 5, Day 29 (±2 days):

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications
- Drug Accountability
- Dispense ibrutinib

7.1.2.2.4 Week 9

The following procedures will be performed at Week 9, Day 57 (±2 days, except for imaging):

Pre-Dose

- Imaging by CT/MRI (must be performed within 7 days prior to first dose of rituximab)
- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - T/B/NK cell counts
  - Biomarkers
- Review of AEs and concomitant medications

Dosing and Post-Dose

- Drug accountability
- Dispense ibrutinib
- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- Review of AEs and concomitant medications

7.1.2.2.5 Weeks 10, 11, 12

The following procedures will be performed on Weeks 10, 11, 12 (±2 days except Week 11):

Pre-Dose

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Week 11 only - Research laboratory blood samples collected 30–60 minutes pre-dose for:
  - PK
  - T/B/NK cell counts
  - Biomarkers
- Review of AEs and concomitant medications

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- PK (Week 11 only); see Section 7.3.20 for timepoints
- Biomarkers (4 hrs after administration of ibrutinib, Week 11 only)
- Review of AEs and concomitant medications
- Dispense ibrutinib (Week 12 only)

7.1.2.2.6 Every 4 Weeks from Week 16 until Treatment Termination

Visits will be performed every 4 weeks (±2 days) starting at Week 16 until completion of the Week 56 Visit and then every 12 weeks (±2 days) thereafter. All visits will be scheduled in

relation to Day 1. Visit windows are relative to the Day 1 visit date. The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 12 weeks from Day 1 [or at the closest associated visit] for women of childbearing potential only)
- Weeks 16 and 20 only - Research laboratory blood samples for:
  - T/B/NK cell counts
  - Biomarkers
- Drug accountability
- Dispense ibrutinib
- Review of AEs and concomitant medications

7.1.2.3 Treatment Termination Visit

The treatment termination visit should be performed at any time during the study, if based on clinical evaluation, the investigator suspects PD, or if the subject discontinues treatment for any other reason. If possible, the visit should be performed within 4 to 24 hours after the subject's previous dose. If the subject comes in for a regular study visit and the investigator wants to discontinue treatment at that time, the regular visit will become the termination visit. Any additional procedures that would not be performed for the regular study visit should be performed for the treatment termination visit.

The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Coagulation

- Research laboratory blood samples collected:
  - T/B/NK cell counts
  - Biomarkers
- CT or MRI (if clinically indicated)
- Optional tumor tissue biopsy (if discontinued treatment due to PD)
- Drug accountability
- Review of AEs and concomitant medications

7.1.2.4 Response Evaluations

Response Evaluation visits will be performed at the following timepoints (per Cheson 2007):

Arm 1: Every 12 weeks from first dose for the first 8 assessments and then every 24 weeks until the subject exhibits disease progression (on or up to 7 days prior to study visit)

Arm 2: At Week 9, Week 20, and then every 12 weeks for 6 assessments after Week 20, and then every 24 weeks until the subject exhibits disease progression (on or up to 7 days prior to study visit)

The following procedures will be performed in conjunction with standard visits as follows:

- Radiologic exam by CT or MRI scan
- PET (repeat to confirm CR if positive at screening, PET will only be done to confirm CR and will not be required thereafter)
- Bone marrow biopsy and/or aspirate for MRD analysis (repeat to confirm CR if positive at screening) and possibly for other biomarkers
- Overall response assessment
- Research laboratory blood samples (when subject achieved CR and/or at PD) for:
  - T/B/NK cell counts
  - Biomarkers

  If the subject discontinues treatment due to PD and the above research laboratory blood samples were collected at the Treatment Termination Visit, the samples do not need to be repeated.
- B-symptom collection (this assessment should be performed at the clinic visit occurring closest to the date of the radiologic exam)

7.1.3 Follow-Up Phase

7.1.3.1 Safety Follow-up

A Safety Follow-up visit should occur 30 days (±7 days) from the last dose of study drug **or** prior to the start of a new anticancer treatment. If the subject starts a new anticancer treatment less than 7 days after the treatment termination visit, only those procedures not conducted at the treatment termination visit should be performed at the Safety Follow-up visit.

Subjects who withdraw consent to treatment may still participate in Safety Follow-up.
The following procedures will be performed at the Safety Follow-up visit:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- 12-lead ECG (in triplicate [≥1 minute apart])
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Coagulation
  - Urinalysis
- Research laboratory blood samples for:
  - Biomarkers
- Review of AEs and concomitant medications

7.1.3.2 Response Follow-Up

Subjects who discontinue the study for reasons other than PD will be followed every 12 weeks (±7 days) from last CT or MRI scan until PD or use of alternative antineoplastic therapy, up to 3 years after the first dose of the last subject enrolled. During this period, scans will be done per investigator discretion.

7.1.3.3 Survival Follow-Up

Once subjects progress or start use of alternative antineoplastic therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 12 weeks (±7 days) from last dose by clinic visit or telephone to assess survival and the use of alternative antineoplastic therapy and stem cell transplant, up to 3 years after the last dose of the last subject enrolled. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

7.2 Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

7.3 Description of Procedures

7.3.1 Medical History

The subject's complete history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis will be recorded. Smoking history and alcohol use will also be recorded.

7.3.2 Physical Examination

The physical examination will include, at a minimum, the general appearance of the subject, examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities and lymphatic system. The musculoskeletal system and nervous system may be included in the examination if clinically indicated.

7.3.3 B-symptoms

The subject will be asked about the occurrence of B-symptoms at Screening and at every Response Evaluation Visit. At Screening, collection of B-symptoms will include unexplained weight loss >10% within the last 6 months, unexplained fever >38°C for at least 3 consecutive days within the last 3 months, and drenching night sweats within the last 3 months. At every Response Evaluation Visit, collection of B-symptoms will include unexplained weight loss >10% within the last month, unexplained fever >38°C for at least 3 consecutive days within the last month, and drenching night sweats within the last month. Any new or worsening of a pre-existing B-symptom should be recorded as an AE.

7.3.4 Vital Signs, Height and Weight

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position for approximately 3 minutes.

Height (screening only) and weight will also be collected.

7.3.5 ECOG Performance Status

The ECOG performance index is provided in Appendix 3.

7.3.6 Electrocardiogram

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

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, it is recommended that ECGs are performed first.

At Screening and at Safety Follow-up, 12-lead ECGs will be done in triplicate (≥1 minute apart); the calculated QTc average of the 3 ECGs must be <470 msec for eligibility.

7.3.7 Prior/Concomitant Medications

All prior/concomitant medications (including over-the-counter, supplements, and herbal products) and procedures will be collected from Screening or from 14 days before the start of study drug, whichever is longer, through the Safety Follow-up visit.

7.3.8 Adverse Events

All AEs whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. Only SAEs will be reported to the Sponsor prior to the first dose of study drug. From the first dose of study drug, AEs/SAEs will be recorded in the eCRFs and will continue until 30 days after the last dose of study drug.

Laboratory abnormalities which result in signs and symptoms, require intervention or follow-up and are considered clinically significant should be recorded as AEs. AEs will be recorded at each visit or as reported during the treatment period.

7.3.9 CT/MRI and PET Scans

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites and a PET scan are required for the pretreatment tumor assessment.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of IV contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

The same radiographic technique used for a subject's pretreatment tumor assessment should be used throughout the course of the study and should be mentioned in each radiology report. The same imaging equipment should be used for all scans, whenever possible.

Following the pretreatment tumor assessments, CT/MRI should be performed as per schedule of assessments (or more often if clinically indicated) and repeat PET scanning will only be required to confirm CR **and** will be performed only if it was positive at Screening. PET will only be done to confirm CR and will not be required thereafter.

De-identified copies of all scans and radiology reports (including those from screening) must be provided to the Sponsor or designee (eg, central imaging vendor). At the Sponsor's discretion, the Sponsor or its designee may conduct an independent review of the investigator responses.

7.3.10 Response Assessment

Response assessments will be completed by the investigator using Cheson 2007. At Screening, up to six target lesions will be selected and will be followed for the duration of the study. All target lesions must be followed and mentioned in the radiology report at all subsequent response assessments (see Appendix 5).

Information on extranodal involvement (eg, gastric or ocular disease) will also be recorded. Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

Caution must be exercised not to confuse a possible tumor flare with progressive disease. Delayed responses after a tumor flare have been reported in follicular lymphoma. In order to accommodate the potential for immune flare (pseudoprogression), treatment with ibrutinib may continue between the initial assessment and confirmation of progression. In the absence of clinically significant deterioration, a biopsy (if lesion is assessable) should be performed at the time of suspected tumor flare (in order to rule out tumor necrosis and/or an inflammatory reaction) or the investigator may continue dosing and a CT/MRI scan and/or biopsy should be performed at least 4 weeks later to confirm PD. Subjects with presumed progressive disease who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive ibrutinib as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion. Ibrutinib should be discontinued if there is confirmed progressive disease per Cheson 2007 criteria or other clinical data suggest clear evidence of progression. such a case, the date of PD will be documented as the evaluation where PD was first suspected.

If progressive disease is ruled out, the subject may resume treatment with ibrutinib (if interruption was <28 days), and a follow-up radiological assessment is recommended within 4–6 weeks, if progression was suspected based on imaging studies. If tumor flare is confirmed by biopsy and the study drug interruption is ≥28 days, subjects may be permitted to continue ibrutinib with approval from the Medical Monitor.

7.3.11 Hematology

Hematology will be done at each scheduled visit.

Hematology studies must include complete blood count with differential and platelet counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.12 Serum Chemistry

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.13 Coagulation

Coagulation includes PT, PTT and INR. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.14 Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.15 Pregnancy Test

A serum pregnancy test will be required at Screening by a local laboratory only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

Urine pregnancy tests should be performed every 12 weeks from Day 1 (or at the closest associated visit), or as clinically indicated, for women of childbearing potential only.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.16 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.3.17 Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy will be done at Screening or up to 28 days before the first dose of study drug. Thereafter, bone marrow aspirate and biopsy will only be required to confirm CR if it was positive at Screening.

Standard clinical testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. Additional samples will be collected for biomarkers and other exploratory evaluations such as for evidence of minimal residual disease (MRD) if methods are available.

7.3.18 T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be taken predose. Percentages and absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD56^+$ and $CD16/56^+$ cells will be collected. Thereafter this testing will be done for Arm 1 and Arm 2 per schedules of assessment.

7.3.19 Blood Samples for Immunophenotypes, Secreted Proteins, and Other Biomarkers

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses. Fluids including blood collected during the course of the study may be used for, but not limited to, pharmacodynamics and biomarker assessments as noted above.

7.3.20 Pharmacokinetics

Plasma PK of ibrutinib in combination with rituximab will be collected in 20 of the total 60 subjects treated in Arm 1. Plasma PK of ibrutinib alone and in combination with rituximab will be collected in all 20 subjects treated in Arm 2.

Refer to Table 3 for the PK sample schedule for Arm 1 and Arm 2.

Table 3: Pharmacokinetic Sample Schedule

Arm	Ibrutinib	Rituximab	Week	Day	Predose	Time After Dosing[a]			
						1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h ± 1 h
1	Continuous	Infusion 3	3	15	x	x	x	x	x
2	Continuous	NA	3	15	x	x	x	x	x
	Continuous	Infusion 3	11	71	x	x	x	x	x

[a] Record actual time of ibrutinib and rituximab administration and sample collection.

7.3.21 Pharmacokinetics Sample Collection for Subjects Treated with Concomitant CYP3A Inhibitors While on Ibrutinib Treatment

For subjects who must take strong or moderate CYP3A inhibitors while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A inhibitor/inducer has started and is still in use. PK samples will be collected at:

- Pre-dose ibrutinib (Sample must be obtained 22–24 hours post the previous day's dose and before dosing on the day of the scheduled visit)
- 1 hour ± 15 min
- 2 hours ± 15 min
- 4 hours ± 30 min

Refer to the laboratory binder for instructions on collecting and processing these samples. On the day of the sampling visit, the subject will not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing.

7.3.22 Tumor Tissue Biopsy

For subjects enrolled in Arm 1, pre-treatment and post-progression tumor biopsies are optional.

For subjects enrolled in Arm 2, pre-treatment biopsy is required and post-progression tumor biopsies are optional.

Tumor samples may be analyzed by GEP, WES, or other methods to define biomarkers that predict response or resistance to ibrutinib therapy.

8. SUBJECT COMPLETION AND WITHDRAWAL

8.1 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.

8.2 Treatment Discontinuation

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

- Confirmed PD
- Unacceptable toxicity: an intercurrent illness or AE that prevents further ibrutinib administration
- Treatment discontinuation by subject
- Investigator decision (such as significant protocol deviation, or best interest of the subject)
- Subject is significantly or routinely noncompliant with the study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo a treatment termination visit and be followed for progression and survival.

It is recommended that the Investigator notifies the Sponsor prior to discontinuing a subject due to any reason. If a subject will be discontinued due to disease progression, the Investigator should provide documentation of disease progression for review by the Sponsor's Medical Monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

8.3 Study Exit/Withdrawal

Exit from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal;
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

9. STATISTICAL METHODS

9.1 General Considerations

This is an open-label, Phase 2 study designed to assess the efficacy and safety of ibrutinib combined with rituximab in previously untreated subjects with FL. The study will include approximately 80 subjects with two treatment arms, a main study Arm 1 with n=~60 subjects and an exploratory Arm 2 with n=~20 subjects.

For the primary and secondary objectives, Arm 1 and Arm 2 will be analyzed separately.

One of the purposes of Arm 2 is to identify biomarkers that predict sensitivity or resistance to ibrutinib. Based on Phase 1 clinical data in FL it is predicted that approximately half of the subjects treated in this arm will show evidence of resistance to single-agent ibrutinib. By providing a lead-in time prior to the initiation of rituximab, pre- and post-progression biopsy samples can be collected to address markers of drug resistance. These objectives are exploratory and therefore the primary and secondary objectives related to clinical efficacy are paramount but will be analyzed separately from Arm 1 since the treatment regimen in this arm is different.

9.1.1 Response Assessment

Response assessments will be done by the investigators. The response criteria are based on the revised criteria for malignant lymphoma described in the revised International Working Group for NHL (Cheson 2007).

9.1.2 Safety Monitoring

The study's investigators and data coordinators are responsible for entering the data and safety of this study, including implementation of the stopping rules for efficacy.

All sites are required to use the eCRFs provided by the study sponsor. All sites will be monitored on an ongoing basis by the study sponsor.

Safety data is monitored in accordance with the sponsor's Pharmacoviligance Committee procedures. AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns.

9.2 Definition of Analysis Populations

The following definitions will be used for the efficacy and safety analysis sets:

- **All-Treated Population:** The subjects who are enrolled in the study and have received at least 1 dose of study drug.
- **Response-Evaluable Population:** The subjects in the all treated population who have measurable disease at baseline and have at least one adequate post-treatment disease assessment by investigator before the start of subsequent anti-cancer therapy.
- **Safety Analysis Population:** All enrolled subjects who receive at least 1 dose of study drug (same as all treated population).

The all treated population will be used for analyzing efficacy endpoints unless specified otherwise, the response evaluable population will be used for sensitivity analysis of efficacy endpoints and the safety population will be used for safety analysis.

9.3 Endpoint Data Analysis

9.3.1 Demographic/Baseline Characteristics and Study Conduct

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease burden, and number of prior therapies) will be summarized by study arm. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.

Further, compliance parameters (including number of doses taken compared with number of doses that should have been taken), the reason for discontinuation, and concurrent treatments will also be similarly summarized.

9.3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate (CR+PR) as assessed by investigators for Arm 1 and Arm 2 separately. The ORR is defined as the proportion of subjects who achieve either a PR or CR as best response as assessed by investigators according to the revised International Working Group Criteria for NHL. Overall response rate will be calculated for the all-treated population for Arm 1 and Arm 2 separately. The corresponding 95% two-sided confidence intervals will be derived.

9.3.2.1 Analysis Methods for Arm 1

The primary analysis for all efficacy endpoints will be conducted based on the all treated population. The all treated population is defined as the subjects who are enrolled in the study and have received at least 1 dose of study treatment. Subjects with no evaluable response will be considered non-responder.

The ORR and its 95% confidence interval (CI) will be calculated using normal approximation to the binomial distribution using Wilson's score method. If the lower bound of the CI around the ORR is greater than or equal to 53%, then it will be concluded that the ORR of the treatment regimen of Arm 1 is superior to the ORR of 53% given by historical control.

9.3.2.2 Analysis Methods for Arm 2

The ORR and its 95% confidence interval will be calculated using normal approximation to the binomial distribution using Wilson's score method. Subjects with no evaluable post-baseline response will be considered as non-responder.

9.3.3 Secondary Efficacy Endpoints

9.3.3.1 Duration of Response

For subjects achieving overall response as assessed by investigators, their duration of response as assessed by investigators will be calculated to determine durability. Duration of response will be measured from the time by which the measurement criteria are met for CR or PR, whichever is recorded first, until death or the first date by which recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Subjects who had the event after the start of subsequent therapy, or are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored at the last tumor assessment on or before the start of subsequent therapy and clinical cut-off time. Subjects with no post-baseline disease assessment will be censored on Day 1.

Data from responders will include subjects who achieve CR or PR based on the revised International Working Group Criteria for NHL response criteria (Cheson 2007). Non-responders will be excluded from the analysis for DOR. Duration of response will be calculated using assessments by investigators and by study arm. Kaplan-Meier methodology will be used to estimate event-free curves, median and 95% CI of median.

9.3.3.2 Progression-free Survival

Progression-free survival will be measured as time from first study drug administration to the first occurrence of lymphoma progression or death from any cause.

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment that occurs before the initiation of alternative anticancer therapy. The estimates will be formed using the all treated population.

Progression-free survival will be calculated using assessments by investigators by study arm. Kaplan-Meier methodology will be used to estimate event-free curves median and 95% CI of median.

9.3.3.3 Overall Survival

The duration of OS will be measured from the time of first study drug administration until the date of death. Kaplan-Meier methodology will be used to estimate overall survival curves and corresponding quartiles (including the median).

Data for subjects who have not died or have exited from the study at the time of clinical-cutoff will be censored at the date of the last known contact. The estimates will be formed using the all treated population.

9.3.4 Safety Analysis

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of ibrutinib. Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported by the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class and Preferred Term. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

AEs requiring discontinuation of study drug will be summarized separately, both overall and by AE severity and by relationship to study drug.

Clinically significant abnormal laboratory values will be summarized. Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to pre-specified imputation rules. The rule will be described in a Statistical Analysis Plan (SAP). No other imputation of values for missing data will be performed.

9.3.5 Pharmacokinetics

Plasma concentrations of ibrutinib and metabolite, for example PCI-45227, will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored.

- Bioanalytical data from this study will be used in noncompartmental PK analysis and also may be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. Pharmacokinetic relationships to pharmacodynamic measures of efficacy or toxicity may also be explored.
- For subjects who received CYP3A inhibitors, as data permits, a comparison of ibrutinib and PCI-45227 plasma concentrations after ibrutinib administration alone and in combination with CYP3A inhibitors will be explored.

9.3.6 Exploratory Analyses

- Change in peripheral T/B/NK count and profiling of immunophenotypes
- Change in secreted protein levels (ie, chemokines, cytokines, growth factors)
- Identification of biomarkers that predict sensitivity or resistance to ibrutinib (ie, GEP, WES, etc.)

Clinically relevant biomarkers may be associated with clinical responses. A Fisher Exact test or other methods may be used to estimate the association between the clinical response rates and each biomarker.

The SAP will provide additional analysis details.

9.4 Handling of Missing Data

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation or contact.

Duration of Response and Progression-free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the date of the initiation of alternative anticancer therapy. Data for subjects who had the event after the start of subsequent therapy, or are progression-free and alive at the time of the clinical data cut-off, or have unknown status will be censored at the last tumor assessment on or before the start of subsequent therapy or clinical cut-off time. Subjects with no post-baseline disease assessment will be censored on Day 1.

Overall Survival: Data for subjects who have not died will be censored at the date of the last study evaluation or contact when subjects are known to be alive.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules and will be pre-defined in a SAP. No other imputation of values for missing data will be performed.

9.5 Determination of Sample Size

The planned sample size for this open-label, Phase 2 study is N=60 subjects which will be enrolled in Arm 1; 20 additional subjects will be enrolled in Arm 2. The hypotheses test of primary endpoint analysis for Arm 1 in this study assumes an underlying response rate of 53% for first-line rituximab treatment in subjects with low grade FL (Hainsworth 2002; Freedman 2009). A sample size of approximately 60 eligible subjects is needed to exclude a 53% response rate at the 1-sided 0.025 significance level with at least 80% power.

9.6 Interim Analysis

No interim analysis is planned.

9.7 Analysis for Study Report

The analyses for the Clinical Study Report (CSR) will occur at least 1 year after the last subject enrolled received the first dose of study drug. Analysis methods will be provided in the SAP.

10. 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.

10.1 Adverse Event Definitions and Classifications

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject after the ICF is signed and for 30 days following the last dose of study drug.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with FL that were not present before the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered an AE:

- **Pre-existing Condition:** A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or Elective Hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

10.1.2 Serious Adverse Event

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

- Results in death (ie, the AE actually causes or leads to death)
- Is life-threatening: "life-threatening" is defined as an AE in which 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. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject, or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

10.1.3 Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

10.1.4 Severity Criteria (Grade 1-5)

Definitions found in the CTCAE (version 4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences that are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences that introduce some level of inconvenience or concern to the subject, and that may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe AE) – experiences that are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment.
- Grade 4 (Life-threatening or disabling AE) – experiences that cause the subject to be in imminent danger of death.

- Grade 5 (Death related to AE) – experiences that result in subject death.

10.1.5 Causality (Attribution)

The investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

10.2 Documenting and Reporting of Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on an SAE Worksheet as outlined in Section 10.2.2.2.

10.2.1 Special Reporting Situations

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

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

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

10.2.2 Adverse Event Reporting Procedures

10.2.2.1 All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All serious events will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. Any SAEs that occur more than 30 days following the last dose of study drug should also be reported if considered related to study drug.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. 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 drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

10.2.2.2 Expedited Reporting Requirements for Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor contact person within 24 hours of knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor using the SAE Form/MedWatch or Council for International Organizations of Medical Sciences (CIOMS), which must be completed by a physician from the study site, and submitted to the Sponsor within 24 hours of when the investigator becomes aware of the event.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a SAE.

If study drug is discontinued due to an SAE, this information must be included in the SAE report.

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

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

10.2.3 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.

10.2.4 Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) following the procedure described above for serious AEs and will require enhanced data collection. **All Adverse Events of Special Interest (AESI) will be submitted from the clinical site to the Sponsor (or designee). If no serious criterion is met, the site should submit the SAE form by selecting the AESI box.**

10.2.4.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 10.2.4 above.

10.2.5 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 AEs and must be reported in a timely fashion. 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 also be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. The pregnant female will be followed for outcome (elective termination of the pregnancy, miscarriage, or delivery) only if she provides a separate written consent. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II.

11. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

11.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to the Sponsor or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

11.3 Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

11.4 Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

11.5 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 11.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with the Sponsor and its designees, regulatory agencies, and IRBs/REBs/IECs. The Sponsor will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

11.6 Study Files and Record Retention

The Investigator **must** keep a record of **all** subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to the Sponsor, or designee, and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify the Sponsor and obtain written approval from the Sponsor before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

The Sponsor must be notified in advance of, and the Sponsor must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the Investigator and the Sponsor to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

11.7 Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within 5 days of each subject's visit. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by the Sponsor or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

11.8 Investigational Study Drug Accountability

Ibrutinib and any comparator used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib or comparator to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from the Sponsor.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of the Sponsor and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1125-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or comparator dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with the Sponsors' requirements. If the site cannot meet the Sponsors' requirements for disposal/destruction, arrangements will be made between the site and the Sponsor or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

11.9 Study Monitoring/Audit Requirements

Representatives of the Sponsor or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

The Sponsor or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other regulatory agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, the Sponsor will be available to assist in the preparation. All pertinent study data should be made available as requested to the regulatory authority for verification, audit, or inspection purposes.

11.10 Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain

IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

11.11 Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

11.12 Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and the Sponsor or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA1572) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify the Sponsor or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

11.13 Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

11.14 Protocol Amendments

The Sponsor will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by the Sponsor before the amendment may take effect at each site. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and the Sponsor.

11.15 Publication of Study Results

The Sponsor may use the results of this clinical study in registration documents for regulatory authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, the Sponsor reserves the right to preview all manuscripts and abstracts related to this study, allowing the Sponsor sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and the Sponsor.

11.16 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11.17 Study Completion

The study is expected to be completed approximately 3 years after the last subject is enrolled and receives the first dose. Subjects who remain on study treatment may have access to the study drug under a long-term protocol or as commercially available product when the study is completed.

12. REFERENCES

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13. APPENDICES

Appendix 1: Schedule of Assessments for Arm 1

Phase	Screening	Treatment							Post-treatment			
Study Week		1	2	3	4	5	9 until Treatment Termination	Response Evaluations	Treatment Termination Visit	Safety Follow-Up	Response Follow-Up (Until PD)	Survival Follow-up (Post PD)
Study Day		1	8	15	22	29	Q4 weeks until completion of Week 49 Visit and then Q12 weeks thereafter	Q12 weeks for the first 8 assessments, then Q24 weeks thereafter	At any time during the study	30 days from last dose or prior to subsequent antineoplastic therapy	Q12 weeks from last CT/MRI scan	Q12 weeks from last dose
Visit Window	*-28 days*		*± 2 days*		*± 2 days*	*± 2 days*	*± 2 days*	*for CT only: on or up to 7 days prior to study visit*	4-24 hours from previous dose	*± 7 days*	*± 7 days*	*± 7 days*
Screening/Administrative												
Informed consent	X											
Confirm eligibility (Inclusion/exclusion criteria)	X	X										
Medical history and demographics	X											
Study Assessments												
Physical exam	X	X	X	X	X	X	X		X	X		
ECOG performance status	X	X	X	X	X	X	X		X	X		
Vital signs and weight (height only at screening)	X	X	X	X	X	X	X		X	X		
12-lead ECG (triplicate)	X									X		
Prior and concomitant medications	Continuous from ICF or 14 days prior the first dose of study drug (whichever is greater) to 30 days after last dose of study drug											
Adverse events		Continuous from ICF to 30 days after last dose of study drug										
Clinical Laboratory Assessments												
Hematology	X	X	X	X	X	X	X		X	X		
Serum chemistry	X	X	X	X	X	X	X		X	X		
Coagulation (PT, PTT, INR)	X								X	X		
Hepatitis serologies	X											
Pregnancy test (serum at screening, urine at f/u)	X	As clinically indicated or Q12 weeks from Day 1 at the closest associated visit (± 2 days)										
Urinalysis	X	As clinically indicated								X		
Efficacy Assessments												
CT/MRI scan, also as clinically indicated	X							X	as clnically indicated		X	
B-symptom collection	X							X				
PET scan	X							Repeat to confirm CR if positive at screening				
Bone marrow aspirate and biopsy (including MRD)	X							Repeat to confirm CR if positive at screening				
Survival status and subsequent antineoplastic therapy												X
Research Laboratory Assessments												
PK (predose, 1,2,4,6 h)				X			if taking CYP3A					
T/B/NK cell counts		X (predose)		X (predose)			X (at week 9 & 13 only)	When subject achieved CR and/or at PD	X			
Biomarkers	X	X (predose & 4h postdose)		X (predose & 4h postdose)			X (at week 9 & 13 only)	When subject achieved CR and/or at PD	X	X		
Tumor tissue biopsy (optional)	X								if discontinued treatment due to PD			
Study Drug Administration												
Dispense ibrutinib		X				X	X					
In-clinic administration of ibrutinib		X	X	X	X							
In-clinic administration of rituximab		X	X	X	X							
Drug accountability						X	X		X			

Appendix 2: Schedule of Assessments for Arm 2

Phase	Screening	Treatment									Post-treatment			
Study Week		1	3	5	9	10	11	12	16 until Treatment Termination	Response Evaluation	Treatment Termination Visit	Safety Follow-Up	Response Follow-Up (Until PD)	Survival Follow-Up (Post PD)
Study Day		1	15	29	57	64	71	78	Q4 weeks until completion of Week 56 Visit and then Q12 weeks thereafter	At Week 9, Week 20, and then every 12 weeks for 6 assessments after Week 20, and then Q24 weeks thereafter	At any time during the study	30 days from last dose or prior to subsequent antineoplastic therapy	Q12 weeks from last dose	Q12 weeks from last dose
Visit Window	*-28 days*			*± 2 days*	*± 2 days except CT*	*± 2 days*		*± 2 days*	*± 2 days*	*for CT only: on or up to 7 days prior to study visit*	4-24 hours from previous dose	*± 7 days*	*± 7 days*	*± 7 days*
Screening/Administrative														
Informed consent	X													
Confirm eligibility (Inclusion/exclusion criteria)	X	X												
Medical history and demographics	X													
Study Assessments														
Physical exam	X	X	X	X	X	X	X	X	X		X	X		
ECOG performance status	X	X	X	X	X	X	X	X	X		X	X		
Vital signs and weight (height only at screening)	X	X	X	X	X	X	X	X	X		X	X		
12-lead ECG (triplicate)	X											X		
Prior and concomitant medications	Continuous from ICF or 14 days prior the first dose of study drug (whichever is greater) to 30 days after last dose of study drug													
Adverse events		Continuous from ICF to 30 days after last dose of study drug												
Clinical Laboratory Assessments														
Hematology	X	X	X	X	X	X	X	X	X		X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X		X	X		
Coagulation (PT, PTT, INR)	X										X	X		
Hepatitis serologies	X													
Pregnancy test (serum at screening, urine at f/u)	X	As clinically indicated or Q12 weeks from Day 1 at the closest associated visit (± 2 days)												
Urinalysis	X	As clinically indicated										X		
Efficacy Assessments														
CT/MRI scan, also as clinically indicated	X				X(-7days)					X	As clinical indicated		X	
B-symptom collection	X									X				
PET scan	X									Repeat to confirm CR if positive at screening				
Bone marrow aspirate and biopsy (including MRD)	X									Repeat to confirm CR if positive at screening				
Survival status and subsequent antineoplastic therapy														X
Research Laboratory Assessments														
PK (predose, 1,2,4,6 h)			X				X		if taking CYP3A					
T/B/NK cell counts		X (predose)	X (predose)		X (predose)		X (predose)		X (at week 16 & 20 only)	When subject achieved CR and/or at PD	X			
Biomarkers	X	X (predose & 4h postdose)	X (predose & 4h postdose)		X (predose)		X (predose & 4h postdose)		X (at week 16 & 20 only)	When subject achieved CR and/or at PD	X	X		
Tumor tissue biopsy (optional at PD)	X										if discontinued treatment due to PD			
Study Drug Administration														
Dispense ibrutinib		X		X	X			X	X					
In-clinic administration of ibrutinib		X	X		X	X	X	X						
In-clinic administration of rituximab					X	X	X	X						
Drug accountability				X	X			X	X		X			

Appendix 3: Performance Status Scores

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

**Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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Appendix 4: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A enzymes are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.1.2.1 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong Inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
telithromycin	pioglitazone
suboxone	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate Inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole [a]	
imatinib	

Inhibitors of CYP3A	Inducers of CYP3A
Weak Inhibitors: cimetidine fluvoxamine **All Other Inhibitors:** chloramphenicol delaviridine diethyl-dithiocarbamate gestodene mifepristone norfloxacin norfluoxetine star fruit	

[a] Based on internal data, 140 mg ibrutinib dosed with voriconazole produces ibrutinib exposures similar to 560 mg ibrutinib dosed alone. Therefore, for this study, if ibrutinib needs to be administered with voriconazole, 140 mg ibrutinib will be dosed.

Table source: http://medicine.iupui.edu/clinpharm/ddis/main-table/

Appendix 5: Guidelines for Establishing Response to Treatment

Response	Definition	Nodal Masses*	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immune-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT		

CR = complete remission, CT = computed tomography, FDG = [^{18}F]fluorodeoxyglucose, PET = positron emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

* Change in target lesion measurement by CT, unless MRI used as the assessment modality for lesions in anatomical locations not amenable to CT

Progressive disease for Non-Hodgkin's lymphoma is characterized by any new lesion or increase by ≥50% of previously involved sites from nadir for example:

- Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of >1 node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis
- Lesions PET positive if FDG-avid lymphoma or PET positive before therapy
- >50% increase from nadir in the SPD of any previous lesions in the liver or spleen
- New or recurrent involvement in the bone marrow
- An increase of ≥50% in blood lymphocytes with ≥5 x 10^9/L B-cells only in setting of enlarging lymph node, liver, or spleen (Note: an isolated elevation of white blood cell count by itself will not be considered progressive disease unless subject becomes symptomatic from this).

Appendix 6: Child-Pugh Score

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

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

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al. "Transection of the oesophagus for bleeding oesophageal varices". The British journal of surgery, 1973;60: 646-9.