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PROTOCOL

TITLE:	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
PROTOCOL NUMBER:	**PCYC-1130-CA**
STUDY DRUG:	IMBRUVICA® (ibrutinib)
IND NUMBER:	102,688
EudraCT NUMBER:	2014-002069-31
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DATE FINAL:	12 May 2014
Amendment 1 Date:	18 August 2014
Amendment 2 Date:	10 May 2016
Amendment 3 Date:	17 February 2017

Confidentiality Statement

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1130-CA entitled "A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic 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:

for [signature] 17FEB2017

Medical Monitor's Signature Date
Lori Styles, MD
Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Number:	PCYC-1130-CA
Study Phase:	3
Study Duration:	Estimated to be 4 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Obinutuzumab will be supplied as 1000 mg/40 mL solution in a single-use vial for intravenous (IV) administration Chlorambucil will be supplied as 2 mg film-coated tablets for oral (PO) administration
Objectives:	**Primary Objective:** To evaluate the efficacy of ibrutinib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab based on the Independent Review Committee (IRC) assessment of progression-free survival (PFS) in subjects with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) **Secondary Objectives**: To compare the treatment groups in terms of the following: *Efficacy* • Overall response rate (ORR) according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria, as assessed by the IRC • Rate of minimal residual disease (MRD)-negative responses • Overall Survival • Hematological improvement measured by platelet and hemoglobin counts • Patient-reported outcomes (PRO) as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire EuroQoL Five-Dimension (EQ-5D-5L) *Safety* • To evaluate the safety and tolerability of ibrutinib in combination with obinutuzumab compared with chlorambucil in combination with obinutuzumab • To evaluate obinutuzumab-related infusion reactions by treatment arm

	Exploratory Objectives: To evaluate the treatment groups in terms of the following: • Event-free survival • Time to next treatment • Clonal evolution - acquisition of new cytogenetic abnormalities • Potential predictive biomarkers of efficacy and/or mechanisms of resistance • Medical resource utilization (MRU) (eg, requirements of hospitalizations, transfusions and use of growth factors) • Sparse pharmacokinetic (PK) characteristics of ibrutinib in patients with CLL or SLL, and which, if any, covariates (eg, age, sex, body size, or race) influence exposure to ibrutinib • Examination of genetic and molecular prognostic markers
Study Design:	This is a Phase 3, multicenter, randomized, open-label study of oral ibrutinib in combination with intravenous obinutuzumab versus oral chlorambucil in combination with intravenous obinutuzumab in subjects with treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma. Eligible subjects will be randomized in a 1:1 ratio to Treatment Arm A or Treatment Arm B: **Arm A: Ibrutinib + Obinutuzumab** Oral ibrutinib 420 mg daily (3 capsules) continuously (until evidence of progressive disease or no longer tolerated by the patient) in combination with obinutuzumab 1000 mg intravenously over 6 cycles: Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by Day 1 only on Cycles 2-6. **Arm B: Chlorambucil + Obinutuzumab** Treatment will be 6 cycles. Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle. Obinutuzumab will be administered intravenously at a dose of 1000 mg, over 6 cycles: given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only on Cycles 2-6. Treatment will be administered up to a maximum of 6 cycles or until disease progression or unacceptable toxicity, whichever occurs first. Approximately 212 subjects will be randomized. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, randomization will be stratified according to: • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 vs 2 • Cytogenetics – will be stratified into one of three categories o del 17p o del 11q without del 17p o others (neither del 17p nor del 11q)

	Assessment of disease response and progression will be conducted in accordance with IWCLL 2008 criteria, with the modification that isolated treatment-related lymphocytosis will not be considered as disease progression, as recommended by the National Comprehensive Cancer Network (NCCN) 2012 guidelines and further defined in Section 7.2.3. During the Pre-PD Phase, subjects will undergo regular scheduled assessments. Response evaluations will be continued every 4 cycles from the initial dose with study drug until Cycle 33 response assessment and then every 6 cycles until disease progression. Subjects randomized to Arm B (chlorambucil in combination with obinutuzumab) who experience IRC-confirmed disease progression can be eligible for access to next-line ibrutinib (cross-over) therapy. Subjects in either arm who discontinue treatment in the absence of disease progression will remain on study until IRC-confirmed disease progression or study closure. All subjects will undergo an End-of-Treatment Visit up to 30 days after discontinuation of randomized treatment (and/or discontinuation of ibrutinib cross-over therapy for subjects randomized to Treatment Arm B) or prior to starting a new anticancer treatment. All subjects then will be followed for survival and subsequent anti-cancer therapies. A summary flow diagram of the study design is found in Section 3.1.1. An independent Data Monitoring Committee (DMC) will monitor the safety of the study.
Population:	Treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma with active disease requiring therapy
Centers:	Multiple, International
Inclusion Criteria: *Refer to* Section 4 *for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* 1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008) 2. Age 65 yrs and older OR if less than 65 years old, must have at least one of the following criteria: a) Cumulative Illness Rating Score (CIRS) >6 b) Creatinine clearance <70 mL/min using the Cockcroft-Gault equation c) Del 17p by FISH or TP53 mutation by PCR or Next Generation Sequencing (NGS) 3. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment: a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia b) Massive, progressive, or symptomatic splenomegaly c) Massive nodes or progressive or symptomatic lymphadenopathy d) Progressive lymphocytosis

	e) Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy f) Constitutional symptoms 4. Measurable nodal disease by computed tomography (CT) *Laboratory* 5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to Screening and randomization: a) Absolute neutrophil count $\geq 1.0 \times 10^9$/L b) Platelet count $>50 \times 10^9$/L 6. Adequate hepatic and renal function defined as: o Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x ULN. o Estimated Creatinine Clearance ≥ 30 mL/min (Cockcroft-Gault) o Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) *Demographic* 7. Men and women ≥ 18 years of age. 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. *Ethics/other* 9. Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study 10. Ability to provide written informed consent and to understand and comply with the requirements of the study 11. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; 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. 12. 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 90 days after the last dose of ibrutinib/chlorambucil or obinutuzumab, and at least 18 months after the last obinutuzumab dose for female subjects.
Exclusion Criteria:	*Concurrent Conditions* 1. Any prior chemotherapy, radiotherapy, small molecule inhibitors including kinase inhibitors, and/or monoclonal antibody used for treatment of CLL or SLL 2. Evidence of central nervous system (CNS) involvement with primary disease of CLL/SLL 3. History of other malignancies, except:

	a) Malignancy treated with curative intent and with no known active disease present for ≥3 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. 4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura 5. Known or suspected history of Richter's transformation 6. Concurrent administration of >20 mg/day of prednisone within 7 days of randomization unless indicated for prophylaxis or management of allergic reactions (eg, contrast) 7. Known hypersensitivity to one or more study drugs 8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 9. Any uncontrolled active systemic infection or an infection requiring systemic treatment that was completed ≤7 days before randomization. 10. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 11. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 12. Known history of human immunodeficiency virus (HIV) or active with hepatitis B virus (HBV) or hepatitis C virus (HCV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 13. Major surgery within 4 weeks of randomization. 14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 15. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization. 16. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. 17. Concomitant use of warfarin or other Vitamin K antagonists. 18. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix C). 19. Lactating or pregnant. 20. Unwilling or unable to participate in all required study evaluations and procedures.

	21. 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)
Study Treatment:	**1:1 Randomization between Arm A & Arm B** **Arm A: Ibrutinib + Obinutuzumab** Oral ibrutinib 420 mg daily (3 capsules) continuously (until evidence of progressive disease or no longer tolerated by the subject) in combination with obinutuzumab 1000 mg intravenously over 6 cycles: Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by Day 1 only on Cycles 2-6. Intravenous obinutuzumab will be administered per Section 5.3.2.3. The first dose of ibrutinib will be taken in the clinic, after which ibrutinib will be issued to the subject as an ongoing 28-day supply for home administration. **Arm B: Chlorambucil + Obinutuzumab** Treatment will be 6 cycles. Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle. Obinutuzumab will be administered intravenously at a dose of 1000 mg over 6 cycles: given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only on Cycles 2-6. Treatment will be administered up to a maximum of 6 cycles or until disease progression or unacceptable toxicity, whichever occurs first. Intravenous obinutuzumab will be administered per Section 5.3.2.3 Chlorambucil will be administered in the clinic on days which coincide with concomitant obinutuzumab (Days 1 + 15 of Cycle 1 and Day1 of Cycles 2-6) and will be issued to the subject for home administration on other occasions (Day 15 of Cycles 2-6). **Next-line ibrutinib monotherapy:** Access to next-line ibrutinib monotherapy (cross-over) for subjects treated in Arm B may be provided after confirmed disease progression (by the IRC) and approval of the medical monitor.
Concomitant Therapy:	*Refer to Section 6 for information on concomitant therapy.* Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), experimental therapy, or radiotherapy is prohibited or as otherwise detailed in Section 6.1.
Safety Plan: *Refer to* Section 10.1.2 *and DMC charter for details.*	The safety of this study will be monitored by an independent Data Monitoring Committee (DMC) as outlined in the DMC Charter and in accordance with the Sponsor's Pharmacovigilance procedures. A safety review of subjects randomized to the ibrutinib and obinutuzumab arm (Arm A) will be conducted after the first six subjects have completed one cycle of treatment.

Statistical Methods and Data Analysis:	Efficacy analyses will be performed using the intent-to-treat (ITT) population. **Primary Efficacy Analysis:** The primary endpoint of this study is progression-free survival (PFS) as assessed by IRC review, according to IWCLL 2008 criteria. PFS will be analyzed comparing the 2 treatment arms using a log-rank test. Distribution of PFS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model. **Secondary Efficacy Analysis:** • Overall response rate: the chi-square test will be used to compare the two treatment arms. • Rate of MRD-negative response: the chi-square test will be used to compare the two treatment arms. • Overall survival: the two treatment arms will be summarized using Kaplan-Meier point estimates • Hematological improvement: the percentage of subjects with hematological improvement in the two treatment arms will be measured and compared using the chi-square test. • EQ-5D-5L: the scores for the five categorical dimensions will be used to compute a single utility score ranging representing the general health status of the subject. The change in utility score from baseline will be summarized. Methods will be detailed in SAP. . **Exploratory Efficacy Analysis:** Descriptive statistics will be used to summarize the exploratory endpoints: • Event-free survival: Non-response is defined as subjects who do not have CR, CR with incomplete bone marrow recovery (CRi), nodular partial response (nPR), or partial response (PR). • Time to next treatment (TTNT) • Clonal evolution • Potential predictive biomarkers of efficacy and/or mechanisms of resistance • Medical resource utilization (MRU) • Genetic and molecular prognostic markers

	Sparse pharmacokinetic (PK) characteristics of ibrutinib will be evaluated based on the plasma concentration data for ibrutinib collected during the study. Population PK analysis will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant population PK model. Available patient characteristics (eg, demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report. **Safety Analysis:** Detailed tabulations of safety data (adverse events, clinical laboratory tests and other safety endpoints) will be summarized by treatment arms for all patients receiving study drug. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.
Interim Analysis	No interim analysis will be performed.
Sample Size Determination	The sample size is calculated based on the following assumptions: • Randomization ratio of 1:1 • Median PFS of 27 months for Arm B (chlorambucil in combination with obinutuzumab) • Target hazard ratio of 0.55, which corresponds to a median PFS of 49.1 months for Arm A (ibrutinib in combination with obinutuzumab). No interim analysis will be performed. Assuming an enrollment rate of 18 subjects per month, approximately 212 eligible subjects will be enrolled to observe 94 PFS events in approximately 36 months from the first subject randomized. On this basis, the study has at least an 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution for PFS.

ABBREVIATIONS

ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADRs	adverse drug reactions
AE(s)	adverse event(s)
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	Analysis of Covariance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1 visit
C1D8	Cycle 1 Day 8 visit
CBC	complete blood count
CD20	cluster of differentiation 20
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CIRS	Cumulative Illness Rating Score
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete remission (response)
CRF	case report form
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
del 17p	deletion of the short arm of chromosome 17
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMR	electronic medical records
EOT	End-of-Treatment Visit
EQ-5D-5L	Euro-QoL five dimension
FC	fludarabine and cyclophosphamide
FCR	fludarabine/cyclophosphamide/rituximab
FcγR	Fc-gamma receptors
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
GCP	Good Clinical Practice
GCLLSG	German CLL Study Group
G-CSF	granulocyte colony-stimulating factor

HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgVH	immunoglobulin heavy-chain variable
iNHL	Indolent non-Hodgkin's lymphoma
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LMWH	low molecular weight heparins
LN	lymph node
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resources utilization
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NHL	non-Hodgkin's lymphoma
NK	natural killer
nPR	nodular partial remission (response)
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PO	per os (oral)
PR	partial response
pre-PD	Pre-progressive disease
PRO	patient- reported outcome
PT	prothrombin time
qd	once daily

QTc	corrected QT interval
REB	Research Ethics Board
RS	Richter's syndrome
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCARs	severe cutaneous adverse reactions
SD	stable disease
SI	standard international units
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
SOC	system organ class
SOP	standard operating procedures
TLS	tumor lysis syndrome
T_{max}	time to maximum drug concentration
TTNT	Time to Next Treatment
ULN	upper limit of normal
USP	United States pharmacopeia convention
WM	Waldenström's macroglobulinemia
ZAP-70	Zeta-chain-associated protein kinase 70

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most frequent form of adult leukemia in the Western world. It is a common and incurable condition, characterized by a distinct diversity of clinical outcomes ranging from indolent to markedly aggressive (Chiorazzi 2005). With an estimated prevalence in the United States of approximately 106,000, it is largely a disease of the elderly. The median age at diagnosis is approximately seventy years and a quarter of patients are aged eighty or over (SEER 2014).

The predominantly elderly and co-morbid population, the incurable nature of the condition and the diversity of disease variants combine to make CLL an important area of clinical research with an urgent need for innovative and novel treatment approaches for many patient sub-types.

Pathologically, CLL is defined by an accumulation of phenotypically distinct mature monoclonal B cells in the blood, bone marrow, and secondary lymph organs. Small lymphocytic lymphoma (SLL) is a condition possessing similar characteristics but *without* lymphocytosis and is essentially a variant of the same underlying disorder as CLL. Clinically, the two similar pathologies constitute one distinct disease (collectively referred to as CLL hereafter) (Muller-Hermelink 2001).

The clinical course of CLL is extremely variable, with a significant proportion of patients requiring no treatment for decades, whilst more urgent intervention is indicated in others, particularly those with progressive, clinically symptomatic disease. Because the majority of patients are asymptomatic at presentation and as there is currently no consensus on the optimal timing for initiation of treatment (Dighiero 1998), International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines have been developed to define the clinical contexts in which treatment should be commenced (Hallek 2008).

The results of clinical studies in previously untreated CLL have demonstrated major advances in therapy over the last decade. The most active regimen described thus far, on the basis of a single-center experience at the MD Anderson Cancer Center (Keating 2005) and subsequent randomized CLL8 trial (Hallek 2010), is the chemoimmunotherapeutic combination of fludarabine, cyclophosphamide and rituximab (FCR). Although numerous subsequent attempts have been made to improve on FCR eg, through the addition of mitoxantrone, alemtuzumab or granulocyte macrophage colony-stimulating factor (Parikh 2011; Bosch 2009; Reynolds 2012), increasing the dose of rituximab (FCR3) (O'Brien 2005), substituting cladribine or pentostatin for fludarabine (Wierda 2012; Bryan 2011),or combining rituximab with bendamustine (Fischer, 2012) so far this remains the most active regimen and regarded as a standard of care for fit first line patients (Hillmen 2010a).

Despite the impressive disease control demonstrable with FCR and FCR-like regimens in optimally selected patient populations, CLL remains a disease predominantly of the elderly, or those with other concomitant medical conditions, who are less able to tolerate fludarabine based approaches. There is, therefore, a clinical need to continue exploration of new treatment options for older patients and those with multiple co-morbidities (Dores 2007; Gribben 2009).

Additionally, CLL is both pathologically and clinically heterogeneous, resulting in many patient sub groups who respond markedly less favorably to currently available treatment strategies, independently of age and comorbidity. In particular, one feature which has consistently been associated with the worst overall prognosis is deletion of the short arm of chromosome 17 (del 17p) and/or a mutation of the TP53 tumor suppressor gene. These abnormalities occur in about 7-10 % of CLL cases at diagnosis (Krober 2002) and this patient subgroup is characterized by rapid disease progression, poor response to therapy and a very limited median overall survival of less than three years (Dohner 2000).

1.1.1. Chronic Lymphocytic Leukemia in Older Patients and/or those with Comorbidity

It is widely acknowledged that older patients with CLL are frequently under-represented in clinical trials (Goede 2011; Thurmes 2008). One dramatically representative example of this generalized phenomenon is the finding that whilst only 15 percent of patients diagnosed with CLL are under the age of 65 (with a median age of treatment initiation of approximately 75 years) (Shanafelt 2013) over two thirds of patients recruited into recent German GCLLSG trials were younger than 64 (Goede 2004; Clifford 2012). There are many similar examples reported in the literature of clinical trials in CLL which are not sufficiently reflective of the overall patient population.

This discordance between clinical trials and clinical practice has resulted in a relative lack of clinical data in the elderly, which in turn has led to uncertainty about optimal treatment for the majority of these patients. There is no generally accepted standard of care in this clinical context and hence a need for experimental approaches which can help both elucidate and expand the therapeutic management of this patient population.

In addition to age per se, concomitant clinical conditions have a major influence on the suitability of older patients for more intensive (fludarabine based) therapy. For example, many trials, such as CALGB 9011 have consistently found that creatinine clearance, rather than age, is the primary predictor of higher toxicity with fludarabine based therapy in patients with CLL (Martell 2002). Given that approximately 40% of individuals aged 70 or greater may have a glomerular filtration rate less than 60 mL/min (Coresh 2003; Iseki 2004), this finding represents a significant restriction of access for the elderly population to many of the most commonly used treatment regimens.

In addition to a widespread incidence of renal impairment, studies on unselected patients with CLL suggest that almost 90% of newly diagnosed individuals have at least one co-morbid condition, with nearly half suffering from a major concomitant disease (such as coronary artery disease, peripheral vascular disease, diabetes mellitus, pulmonary disease etc) (Thurmes 2008). This is undoubtedly of clinical significance, as the presence of two or more co-morbid conditions was clearly shown to impair treatment response to fludarabine or chlorambucil and shorten progression-free survival (PFS) and overall survival (OS) in elderly patients in the large, randomized GCLLSG CLL5 trial (Eichhorst 2009a).

Those with a Cumulative Illness Rating Score (CIRS) score ≤6 and preserved renal function (creatinine clearance ≥70 mL/min) are generally candidates for more aggressive therapy whereas patients with higher CIRS scores are considered to be less fit and therefore suitable only for less demanding treatment strategies (Eichhorst 2009b). This conceptual therapeutic divide has recently been validated to a certain extent by findings from a study conducted by the Australian CLL Study Group, in a cohort of fit CLL patients age ≥65 (median age, 72). This trial found no difference in the frequency of Grade ≥3 adverse events among individuals with a CIRS score of 0-2, 3-4, or 5-6, supporting the proposition that a CIRS score ≤6 identifies patients able to tolerate more aggressive treatment (Mulligan 2012).

1.1.2. Treatment Options in Older Patients and/or those with Comorbidity

Older patients and/or those with comorbidity who require therapy are only suitable for non-aggressive strategies and are frequently managed with single agent chlorambucil (CLL Trialists' Collaborative Group 1999; Catovsky 2011) or more recently, bendamustine (Knauf 2009a; Knauf 2009b). Responses are achievable in about three quarters of patients, although complete response rates are low, particularly with chlorambucil, where they are very infrequent. Median PFS is also short, typically less than two years.

There appears therefore to be no one single agent offering adequate clinical outcomes in patients with comorbid complications to their CLL diagnosis (Rai 2000). Attempts to address the inadequacies of monotherapy in this patient population have led to assessment of the relatively more intensive combination of chlorambucil and rituximab anti-CD20 therapy.

The superior results of this combination to that achievable with alkylating agent monotherapy alone were eventually confirmed in a pivotal GCLLSG trial, in elderly patients (median age 73 years) with significant co-morbidities. This study examined randomized chlorambucil monotherapy versus chlorambucil combined with rituximab versus chlorambucil combined with obinutuzumab, a third generation type II anti-CD20 antibody (Goede 2014). The addition of rituximab to chlorambucil doubled the response rate and PFS (16 months vs 11 months), without increasing the rates of infection or other complications. Of note however, the combination of chlorambucil and obinutuzumab appeared even more effective, with a PFS of 26.7 months.

The results achievable with chlorambucil combined with anti-CD20 therapy, and particularly with obinutuzumab, therefore offer significant improvements over alkylating agent monotherapy, in patients unable to tolerate fludarabine based alternatives.

There remains therefore a pressing need in patient populations such as the one in the current trial, of older patients and those who have co-morbidities precluding intensive fludarabine based approaches, for newer regimens offering improved outcomes over the best currently available therapy, which appears to be chlorambucil in combination with obinutuzumab.

In view of the promising potential superiority of ibrutinib over chlorambucil the expectation of the current trial is that the combination of ibrutinib with obinutuzumab will result in a significant advance in disease control, beyond that which is possible with existing approaches, thus providing an important additional treatment option for the currently underserved majority of CLL patients.

1.1.3. Chronic Lymphocytic Leukemia with 17p Deletion and/or TP53 mutation

Apart from age and co-morbidity, a number of intrinsic genetic and molecular abnormalities have been characterized which also identify subgroups of CLL patients who generally have an adverse clinical course and a poor outcome to therapy. These include del 17p, del 11q, IgVH unmutated status, use of the IGHV3-21 gene segment and expression of either ZAP70 or CD38 (Krober 2002; Krober 2006). However, it is widely acknowledged that chromosomal 17p deletion is the pre-eminent adverse prognostic parameter, with the majority of patients belonging to an "ultra–high-risk" group characterized by the worst possible overall outcome (Stilgenbauer 2010).

Approximately 10% of patients with CLL in the first line treatment setting carry the del 17p abnormality (Dohner 2000). As the TP53 tumor suppressor gene, which plays a critical role in oncogenesis and response to DNA damaging chemotherapy (Hollstein 1991; Pietsch 2008) is located on the short arm of chromosome 17, over eighty per cent of del 17p deletions are also associated with concomitant p53 dysfunction of some sort (Rossi 2009).

The associated loss of p53 integrity may explain why the del 17p abnormality is the poorest prognostic factor for CLL. So integral in fact is the del 17p/TP53 axis to determining chemoresponsiveness in CLL, that it has been postulated as the only biomarker currently available for driving treatment decisions in the management of the disease (Mertens 2014).

The presence of a TP53 mutation can however also occur in the absence of a del 17p chromosomal abnormality, in approximately five percent of cases of CLL (Rossi 2009; Dicker 2009) and is an equally poor prognostic factor, independent of 17p status (Zenz 2008; Oscier 2002).

Both 17p deletion and TP53 mutation are therefore powerful prognostic markers for non-response to currently available CLL therapy. Patients with these abnormalities have exceptionally poor outcomes with chemoimmunotherapy regimens such as FCR, due in large part to lack of p53 function, which is an important pathway for mediating the cytotoxicity of many drugs, including purine analogs, such as fludarabine (Dohner 1995).

Combination treatment strategies involving newer agents under investigation with anti-CD20 therapy could translate into clinically meaningful improvements in the management of del 17p disease, if these were to result in a higher proportion of responses than appears possible with currently available treatment regimens.

1.1.4. Role of BTK in CLL

One unique particularly promising p53 independent strategy under investigation for the management of del 17p CLL involves selective inhibition of Bruton's tyrosine kinase (Btk), which is an enzyme required for B-cell receptor (BCR) signaling.

Ibrutinib is a potent and selective inhibitor of Btk, resulting in downstream blockade of BCR signaling pathways and arrest of B-cell proliferation. Ibrutinib monotherapy has shown dramatic efficacy in both the first line and relapsed CLL context. In particular, activity appears to be independent of prognostically adverse factors, including del 17p, where response rates in both first line and relapsed disease have been broadly comparable between patients with and without a del 17p abnormality.

In view of the existing clinical findings with ibrutinib there is therefore a strong expectation that in the current trial, the combination of ibrutinib and obinutuzumab, will demonstrate significant first line clinical activity in those patients with del 17p and/or TP53 mutations.

1.2. Ibrutinib Overview

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.

Ibrutinib has been approved in many regions, including the US and EU, for indications including 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/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia (WM), and patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, in vitro and in vivo preclinical activity, and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1. Summary of Nonclinical Data

1.2.1.1. 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).

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

1.2.1.2. Safety and Toxicology

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 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 studies in pregnant rats and rabbits, ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current ibrutinib IB.

1.2.2. Summary of Clinical Data

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

1.2.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours.

Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. 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.

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the ibrutinib IB.

1.2.3. Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided below. For more comprehensive safety information please refer to the current version of the ibrutinib IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.2.3.1. Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia		

1.2.3.2. 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, which included 1 randomized-control study, are summarized below. 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).

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

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
	Hypertension	

1.2.4. Risks

1.2.4.1. 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, subdural 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 6.2.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures. In an in vitro platelet

function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 6.2.3.

1.2.4.2. 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 (eg, 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 5.3.1.4).

1.2.4.3. 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.

1.2.4.4. 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 5.3.1.4).

1.2.4.5. 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. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.2.4.6. 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.

1.2.4.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. 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 including erythema, urticaria, and angioedema have been reported.

1.2.4.8. 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.

1.2.4.9. 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 5.3.1.4).

1.2.4.10. 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. For subject and ibrutinib management guidance, refer to Section 5.3.1.4.

1.2.4.11. 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 eg, >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. This pharmacodynamic effect was less prominent or not observed in other indications.

For subject and ibrutinib management guidance, refer to Section 5.3.1.4.

1.2.4.12. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting

ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3. Obinutuzumab

1.3.1. Summary of Nonclinical Data

For the most comprehensive nonclinical and clinical information regarding obinutuzumab, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.3.1.1. Nonclinical Pharmacology

Nonclinical in vitro studies show that obinutuzumab mediates superior induction of direct cell death and effect or cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) on a panel of NHL cell lines as compared to the Type I CD20 antibodies rituximab and ofatumumab. Its potency to mediate complement-dependent cytotoxicity (CDC) is significantly reduced as compared to these two antibodies. In ex vivo autologous whole blood B-cell depletion studies with blood from healthy volunteers as well as CLL patients, obinutuzumab mediated superior B-cell depletion when compared with rituximab.

These properties of obinutuzumab translated into superior anti-tumor efficacy in direct comparison to rituximab against a number of aggressive subcutaneous and disseminated NHL xenograft models. Obinutuzumab induced complete tumor remission and long term survival (cures) and increased the overall survival in disseminated NHL xenograft models. The efficacious and optimal dose range of obinutuzumab in xenograft models was in the range of 10-30 mg/kg, corresponding to trough levels of 300-600 µg/mL. In addition, obinutuzumab showed efficacy in combination with classical chemotherapeutic agents, such as chlorambucil, fludarabine and bendamustine. Importantly, the combination of obinutuzumab with chemotherapeutic agents was superior to the combination of these agents with rituximab. Treatment with obinutuzumab also resulted in potent and superior depletion of B-cells in the peripheral blood and in lymphoid tissues of hCD20 transgenic mice and cynomolgus monkeys. Vaccination studies in cynomolgus monkeys and human CD20 transgenic mice showed that the enhanced efficacy in terms of B-cell depletion of obinutuzumab translated into suppression of de novo antibody responses, but left the protective humoral memory responses intact.

The data generated to date imply that obinutuzumab represents a novel therapeutic CD20 antibody with outstanding efficacy compared to classical Type I and non-ADCC enhanced CD20 antibodies, such as rituximab and ofatumumab. Based on these non-clinical data it can be anticipated that the combination of the recognition of a Type II epitope together with improved ADCC and ADCP potency exclusive to obinutuzumab may translate into superior clinical efficacy.

1.3.1.2. Toxicology and Safety Pharmacology

The safety and toxicity of obinutuzumab following weekly repeated IV administrations were studied in adult cynomolgus monkeys for up to 26 weeks. The cynomolgus monkey was selected as the species of choice in the safety assessment of obinutuzumab based on a high target sequence homology, comparable target binding affinities and Fc-mediated effector function. Overall, treatment resulted in the expected pharmacological reduction in circulating B lymphocytes and lymphoid depletion of B-specific areas in the spleen and lymph nodes. Moreover, the transient reduction of natural killer (NK) cells after treatment was most likely related to the mechanism of action (FcγRIIIa binding).

Hypersensitivity reactions were noted at all dose groups in the 26-week study and attributed to the foreign recognition of the drug construct in cynomolgus monkeys. These reactions led to unscheduled termination of 6 animals. Due to species differences in protein structure and the perceived foreignness of the drug construct in cynomolgus monkeys, hypersensitivity reactions are not considered relevant in terms of predicting potential immunogenicity of obinutuzumab in humans. Opportunistic infections were suspected in three animals on study and considered a possible secondary result of B-cell depletion. Given its anticipated mode of action resulting in profound B-cell depletion, obinutuzumab is likely associated with an increased risk of infections. However, based on some histomorphological similarities (ie, inflammation/infiltration in various organs) between these three animals and the animals with hypersensitivity reactions in the 26-week study, a hypersensitivity reaction cannot be completely ruled out for these three animals.

Although obinutuzumab as a typical IgG antibody is unlikely to induce off-target related pharmacological effects, a detailed assessment of potential effects on the nervous system, respiration and cardiovascular effects was included in primate studies. No effects were seen after the first dose or following chronic exposure. In cynomolgus monkeys, obinutuzumab did not affect reproductive parameters, embryo fetal development, parturition, postnatal survival, or growth and development of infants.

1.3.2. Summary of Clinical Data

1.3.2.1. Clinical Pharmacology

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies, in patients with CLL or NHL. These studies include Phase 1 and 2 monotherapy studies (BO20999 and BO21003), a Phase Ib combination study (BO21000) and a Phase 3 combination study (BO21004). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis. Population PK modeling was undertaken on all available serum concentration data from studies BO20999, BO21003, BO21000 and BO21004/CLL11 to provide a robust description of the PK behavior of obinutuzumab. This demonstrated that a two compartment PK model comprising both a linear clearance pathway and a non-linear time varying clearance pathway adequately described serum

obinutuzumab concentration data. The initial clearance of obinutuzumab was 2.85 times higher than the steady state clearance which is consistent with a decrease in the time varying clearance component, which is high at the start of treatment and which declines with repeated cycles of obinutuzumab treatment. The time varying clearance pathway is consistent with target mediated drug disposition, such that at the start of treatment when there is a large quantity of CD20 positive cells, this binds obinutuzumab. With repeated dosing of obinutuzumab this saturates the pool of CD20 positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies, and is therefore independent of CD20 positive cells. This analysis further supports the need to minimize the time varying clearance component quickly, and has led to the proposed dose and regimen of 1000 mg in both induction and extended treatment. In the Phase 2 part of study BO21003, which investigated the 1000 mg obinutuzumab dose taken into Phase 3, the PK of obintuzumab was assessed in patients with indolent non-Hodgkin's lymphoma (iNHL) who received weekly administrations of 1000 mg of obinutuzumab during the induction phase (4 administrations; Cycle 1 – Cycle 4) followed by an extended maintenance treatment phase of 1000 mg obinutuzumab every 2 months until disease progression. The mean obinutuzumab serum concentration increased markedly over the 4 treatment cycles. Following the final (ie, fourth) administration of the induction treatment, obinutuzumab serum levels decreased. Overall, mean C_{trough} serum levels of obinutuzumab observed during the maintenance regimen were similar across the 12 maintenance cycles.

In study BO21004/CLL11, a pivotal Phase 3 study in CLL patients, mean serum obinutuzumab concentrations increased from Cycle 1 to Cycle 2 following administration of obinutuzumab on Day 1/2 (45 patients in Stage 1a received the first 1000 mg dose over 2 days: 100 and 900 mg on Days 1 and 2, respectively), Day 8 and Day 15 of Cycle 1. From Cycle 3 until Cycle 6, pre- and post-infusion serum concentrations remained constant during the course of treatment. Having the first 1000 mg administered over 2 days did not impair the rapid minimization of the time varying clearance component indicative of depletion of $CD20^+$ tumor cells.

1.3.2.2. Clinical Efficacy - CLL

In the monotherapy setting, no CRs were observed among 38 patients with relapsed CLL. However, in study BO20999, 8/13 patients (62%) in Phase I and 3/20 patients (15%) in Phase 2 had a PR at the end of treatment.

In the chemotherapy combination study BO21004 (Stage 1a), 71/118 patients (60.2%) in the chlorambucil arm and 52/238 patients (21.8%) in the obinutuzumab + chlorambucil arm experienced a PFS event (death or disease progression). The addition of obinutuzumab to the chlorambucil regimen significantly prolonged PFS when compared to chlorambucil alone ($p < 0.0001$, log-rank test). Overall, 27% of patients in the chlorambucil arm and 84% of patients in the chlorambucil + obinutuzumab arm were progression–free at one year. The risk of having a PFS event (progression or death, whichever occurred first) as assessed by the investigator was statistically significantly decreased for patients treated with obinutuzumab + chlorambucil (stratified hazard ratio [HR] 0.14, 95% CI: 0.09, 0.21). The Kaplan–Meier estimated median PFS

was 10.9 months in the chlorambucil arm and 23.0 months in the obinutuzumab + chlorambucil arm [5.14 - 5.16].

1.3.3. Summary of Clinical Safety

Up to 1 January 2014, an estimated 2409 patient are available for safety analysis of obinutuzumab in clinical trials. These include patients with CLL or NHL, from doses of 50 mg to 2000 mg in monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil. To date, the largest and most mature dataset available to assess the safety of obinutuzumab as monotherapy comes from studies BO20999 and BO21003; the largest and most meaningful dataset to assess the safety of obinutuzumab in combination therapy with chlorambucil comes from study BO21004. Overall, most of the safety experience is based on NHL patients currently undergoing treatment with 1000 mg obinutuzumab; however these data currently remain blinded and therefore contribute little to the assessment of the safety profile of obinutuzumab. There is only limited post marketing experience.

The following adverse events are considered as important risks associated or potentially associated with obinutuzumab: Infusion related reactions, tumor lysis syndrome, thrombocytopenia including acute thrombocytopenia, neutropenia, late onset and prolonged neutropenia, prolonged B-cell depletion, infections including Progressive multifocal leukoencephalopathy and hepatitis B reactivation, gastro-intestinal perforation, worsening of pre-existing cardiac conditions, impaired immunization response, immunogenicity, and second malignancies. Most of these are briefly discussed.

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were infusion-related reactions (IRR); these occurred predominantly during the first infusion. The incidence and severity of infusion related symptoms decreased substantially with subsequent infusions, with most patients having no IRRs during the second and subsequent administrations of obinutuzumab. Patients with a high tumor burden (ie, high peripheral lymphocyte count in CLL (>25 x 10^9/L) may be at increased risk of severe IRR. The commonly experienced IRRs are characterized by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, and fatigue, among other symptoms. In the majority of patients, IRRs were mild or moderate and could be managed. Hypersensitivity may be difficult to distinguish from infusion-related reactions; anaphylaxis has been reported in patients treated with obinutuzumab.

1.3.3.1. Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is considered as adverse drug reaction of obinutuzumab and fatal TLS have been observed among obinutuzumab exposed patients. Patients who are considered to be at risk of TLS (eg, patients with a high tumor burden or a high circulating lymphocyte count) should receive adequate tumor lysis prophylaxis with allopurinol and hydration prior to the infusion of obinutuzumab (Section 5.3.2.2).

1.3.3.2. Neutropenia

Neutropenia and thrombocytopenia are also considered as adverse drug reactions of obinutuzumab. Febrile neutropenia during treatment has been reported with obinutuzumab. The neutropenia resolved spontaneously or with use of colony-stimulating factors. Patients who experience grade 3/4 neutropenia should be closely monitored. Primary prophylaxis with granulocyte colony stimulating factors (G-CSF) is recommended as per the ASCO, EORTC, and ESMO guidelines, namely in patients who are ≥60 years and/or with comorbidities.

1.3.3.3. Thrombocytopenia

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. In CLL patients exposed to obinutuzumab in combination with chlorambucil, fatal hemorrhagic events have also been reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (ie, platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

1.3.3.4. Infections

With regard to the risk of infections, due to the pharmacodynamics effect of obinutuzumab, resulting in profound B cell depletion, obinutuzumab may be associated with an increased risk of infections. Obinutuzumab should not be administered in the presence of a severe infection and caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections.

In particular given that other anti-CD20 antibodies have been associated with hepatitis B reactivation in subjects with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure, or in subjects who are carriers (HBsAg negative and hepatitis B core antibody positive). The incidence of reactivation can be exacerbated, particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy. Hepatitis B virus (HBV) screening should always be performed before initiation of treatment with obinutuzumab as per institutional guidelines. Patients with active Hepatitis B disease should not be treated with obinutuzumab.

Given the profound B cell depletion following exposure to obinutuzumab and a possible pharmaceutical class effect, the risk of PML may be exacerbated among exposure patients. The

diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (CSF testing for JC viral DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

1.3.3.5. Cardiac Disease

In patients with underlying cardiac disease and exposed to obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure and arrhythmias, including atrial fibrillation and tachyarrhythmia have been observed. These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

1.3.4. Guidance for the Investigator

Potential risks of clinical relevance identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia and neutropenia, and infection.

1.3.4.1. Risk of IRR

The most frequently observed IRRs were characterized primarily by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, dyspnea and fatigue. IRRs occurred predominantly during the first infusion, and their incidence and severity decreased rapidly with subsequent infusions. Some patients developed severe IRRs requiring permanent discontinuation of obinutuzumab. Although inconclusive, IRRs appear to be more frequent and/or more severe in patients with large tumor volume (eg, peripheral lymphocytosis, diffuse bone marrow involvement, bulky or high tumor masses). This is most predominantly the case in CLL, but may also be present in other forms of lymphomas. All patients should be premedicated as recommended in the study protocols. Patients who develop IRRs should receive supportive care, and if necessary the infusion should be slowed, interrupted, or split over 2 days.

1.3.4.2. Risk of Tumor Lysis Syndrome

Cases of TLS have been reported in patients receiving obinutuzumab. Patients with a high tumor burden may be at increased risk of TLS. Aggressive intravenous (IV) hydration is the

cornerstone of prevention of TLS and is recommended prior to therapy in all patients at intermediate or high risk for TLS.

Prior to initiation of treatment, dehydration and reversible forms of renal insufficiency (eg, volume contraction, hypercalcemia, urinary tract obstruction) should be corrected. In addition, patients considered to be at risk of TLS should be premedicated with allopurinol starting 2-3 days prior to the first obinutuzumab infusion (Section 5.3.2.2).

1.3.4.3. Risk of Thrombocytopenia and Neutropenia

Some patients treated with obinutuzumab developed Grade 3 or 4 thrombocytopenia or neutropenia, including febrile neutropenia. Patients with febrile neutropenic events should receive IV antibiotics and should be monitored until their neutrophil counts return to a level of ≤Grade 2. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is recommended in NHL patients who are ≥60 years old and/or have comorbidities.

1.3.4.4. Risk of Infection

Consistent with its mode of action resulting in profound B-cell depletion, obinutuzumab has been associated with an increased risk of infections. Obinutuzumab should not be administered in the presence of active severe infections. Physicians should exercise caution when treating patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Particular attention should be given to patients who have had significant prior immunosuppressive treatment, such as high-dose chemotherapy or a stem cell transplant. Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.

One patient experienced progressive multifocal leukoencephalopathy (PML) approximately 2 years after discontinuing obinutuzumab treatment. Physicians should be aware of symptoms suggestive of PML and consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI) and lumbar puncture.

1.4. Study Rationale

This randomized, multicenter, open-label, Phase 3 study is designed to evaluate whether the combination of ibrutinib and the anti-CD20 antibody obinutuzumab will result in superior efficacy, when compared to the combination of chlorambucil and obinutuzumab, in the first line treatment of patients not suitable for intensive (fludarabine based) chemo-immunotherapy by virtue of age, co-morbidity or presence of del 17p.

There are currently no data directly comparing ibrutinib and chlorambucil in the first line treatment of CLL (although a Phase 3 study, RESONATE 2, is ongoing in this setting)

(Burger 2013a). However data in 31 treatment-naïve patients (median age 71 years) from a recently completed trial of ibrutinib in CLL have shown a 71% overall response rate, with 13% of patients recording a complete response (CR) (O'Brien 2014). In addition to the highly encouraging response rate, the estimated 22 month PFS and OS in this patient group treated with ibrutinib were both 96%. To date, these are the best reported outcomes for single agent first line therapy in this particular patient population (Brown 2014), and contrast particularly favorably with chlorambucil, where complete responses are very rarely reported. Furthermore, clinical activity with ibrutinib appeared to be independent of factors generally predictive of a poor response to therapy, including del 17p.

It is therefore reasonable to conclude that ibrutinib will also prove superior to chlorambucil in the first line context and by inference that the combination of ibrutinib and obinutuzumab will have greater clinical activity than the combination of chlorambucil and obinutuzumab in the first line setting of the current trial.

2. STUDY OBJECTIVE

2.1. Primary Objective

To evaluate the efficacy of ibrutinib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab based on the Independent Review Committee (IRC) assessment of PFS. Efficacy will be evaluated according to IWCLL 2008 criteria with modification for treatment-related lymphocytosis, in subjects with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

2.2. Secondary Objective(s)

To compare between the treatment groups in terms of the following:

Efficacy

- Overall response rate (ORR) according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria, as assessed by the IRC
- Rate of minimal residual disease (MRD)-negative responses
- Overall Survival
- Hematological improvement measured by platelet and hemoglobin counts
- Patient-reported outcomes (PRO) as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire EuroQoL Five-Dimension (EQ-5D-5L)

Safety

- To evaluate the safety and tolerability of ibrutinib in combination with obinutuzumab compared with chlorambucil in combination with obinutuzumab

- To evaluate obinutuzumab-related infusion reactions by treatment arm

2.3. Exploratory Objectives

- Event free survival
- Time to next treatment
- Clonal evolution - acquisition of new cytogenetic abnormalities
- Potential predictive biomarkers of efficacy and/or disease-related mechanisms of resistance
- Medical resource utilization (MRU) (eg, requirements of hospitalizations, transfusions and use of growth factors)
- Sparse pharmacokinetic (PK) characteristics of ibrutinib in subjects with CLL or SLL, and which, if any, covariates (eg, age, sex, body size, or race) influence exposure to ibrutinib
- Examination of genetic and molecular prognostic markers

3. STUDY DESIGN

3.1. Overview of Study Design

This is a randomized, multicenter, open-label, Phase 3 study designed to evaluate the safety and efficacy of ibrutinib in combination with obinutuzumab, when compared to chlorambucil in combination with obinutuzumab, in subjects diagnosed with CLL or SLL, who are treatment-naive but now require active therapy.

Approximately 212 subjects will be randomized. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, randomization will be stratified according to:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 vs 2
- Cytogenetics - will be stratified into one of three categories
  - del 17p
  - del 11q without del 17p
  - others (neither del 17p nor del 11q)

Subjects randomized to Arm B will be eligible, upon disease progression (confirmed by IRC) which meets the criteria for treatment (Hallek 2008), to receive ibrutinib monotherapy as next line treatment with approval of medical monitor.

Subject participation will include a Screening Phase, a Pre-PD Phase, and a Follow-up Phase.

The **Screening Phase** will be up to 30 days prior to randomization during which the subject's eligibility and baseline characteristics will be determined.

The **Pre-progressive Disease (Pre-PD) Phase** will extend from randomization to disease progression, death, or the subject meets any criteria specified in Section 9.3, whichever occurs first.

Subjects randomized to **Arm A (ibrutinib in combination with obinutuzumab)** will receive the following regimen:

- **Ibrutinib** will be given orally at a dose of 420 mg daily (3 capsules) until disease progression or unacceptable toxicity.
- Treatment will be intravenous **obinutuzumab** at a fixed dose of 1000 mg, given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only of subsequent cycles, for up to **six** cycles.

Intravenous obinutuzumab will be administered per Section 5.3.2.3. The first dose of ibrutinib will be taken in the clinic, after which ibrutinib will be issued to the subject as an ongoing 28-day supply, for home administration.

Subjects randomized to **Arm B (chlorambucil in combination with obinutuzumab)** will receive the following regimen:

- Treatment will be **6** cycles. **Chlorambucil** will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle.
- **Obinutuzumab** will be administered intravenously at a fixed dose of 1000 mg, given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only of subsequent cycles.

Intravenous obinutuzumab will be administered per Section 5.3.2.3. Chlorambucil will be administered in the clinic on days which coincide with concomitant obinutuzumab (Days 1 + 15 of Cycle 1 and Day1 of Cycles 2-6) or will be issued to the subject for home administration on other occasions (Day 15 of Cycles 2-6).

During the Pre-PD phase, all subjects will undergo regular scheduled assessments as detailed further in Section 7 of the protocol. Response evaluations will be continued every 4 cycles from the initial dose of study drug until Cycle 33 response assessment and then every 6 cycles until disease progression.

Assessment of response and progression will be conducted in accordance with the IWCLL 2008 criteria with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will **not** be considered progressive disease (Section 1.2.4.11). The Investigator will evaluate sites of disease by radiological imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, disease-related symptoms and bone marrow examinations (where appropriate). The same methods of assessment used to assess disease at baseline should be used throughout the study. A central laboratory will perform all hematology, serum chemistry, baseline and post-treatment bone marrow assessments for the primary endpoint analysis.

The primary efficacy analysis will be based on assessment from **an Independent Review Committee** (IRC). As part of the IRC review, radiographic evaluations assessed by independent central radiologists, findings from physical examinations performed by investigators, and hematology results from a central laboratory will be provided. Detailed procedures will be described in a separate charter.

An independent Data Monitoring Committee (DMC) will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures will be provided in a separate charter. The DMC will review the safety data periodically and provide recommendations according to the charter.

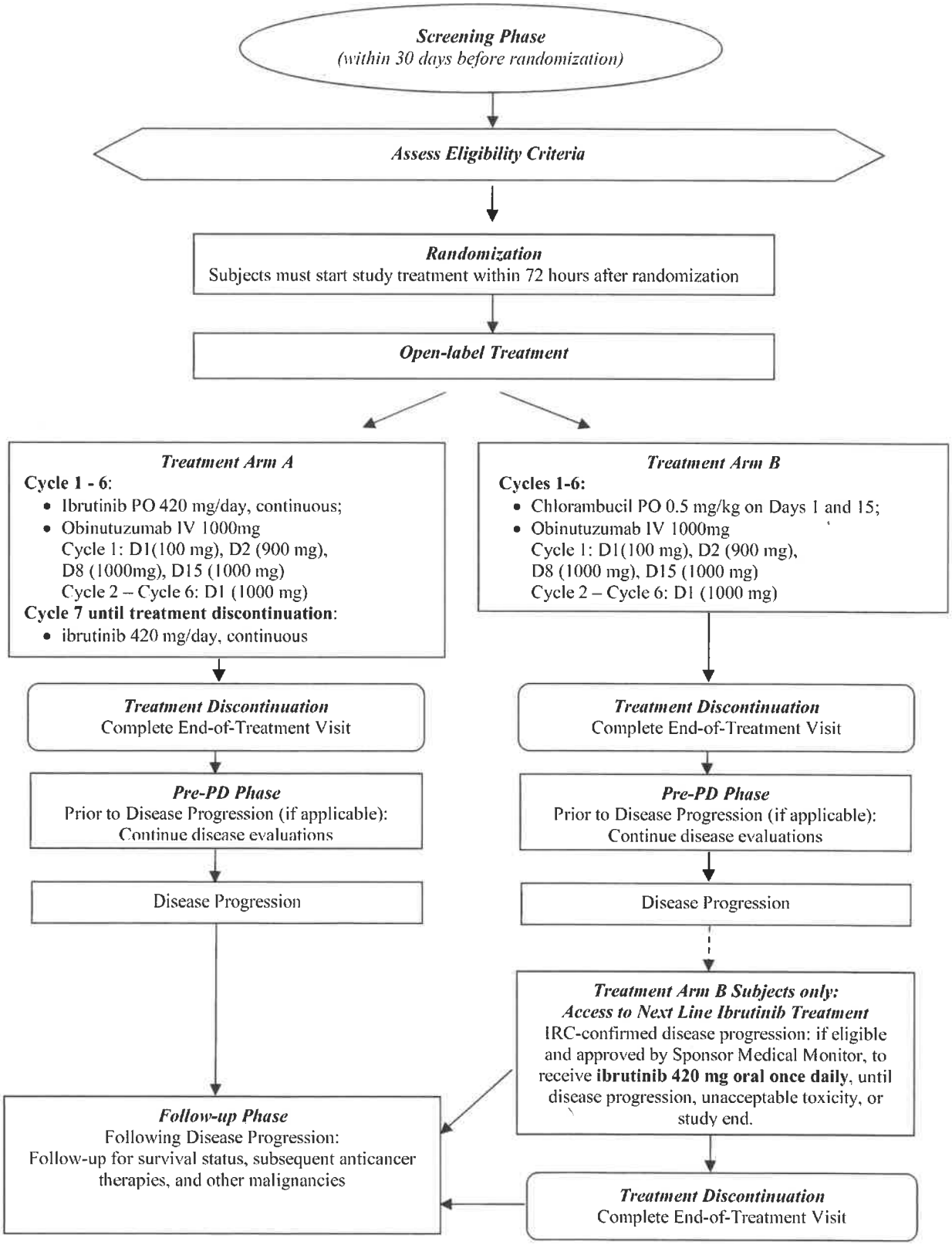
The **Follow-up Phase** will begin once a subject has progressive disease. In this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, occurrence of additional malignancy and patient survival status will be recorded.

Subjects randomized to Arm B (chlorambucil in combination with obinutuzumab), who are eligible upon IRC-confirmed progression for ibrutinib monotherapy (as detailed in Section 8.4) can receive ibrutinib orally at a dose of 420 mg daily (3 capsules) continuously until determined otherwise by the investigator.

The Follow-up Phase will continue until death, loss to follow up, consent withdrawal, or study closure, whichever occurs first. It is important that survival status be assessed and that the date of death is documented for each subject randomized to treatment, regardless of whether or not the subject received treatment.

The Sponsor will continue to follow the subjects for approximately 4 years after the first subject was enrolled to strengthen the collection of mature data, even if the study is completed prior to this date. A long-term extension study may be made available for active patients who choose to continue ibrutinib on a clinical protocol when access to commercial ibrutinib is not feasible.

3.1.1. Study Schema



3.2. Study Design Rationale

3.2.1. Selection Rationale for Ibrutinib Combined with Obinutuzumab

Obinutuzumab is a humanized type II anti-CD20 antibody, the Fc portion of which has been glycoengineered to reduce fucosylation, resulting in optimized affinity for the FcγRIIIa receptor and enhanced antibody-dependent cellular cytotoxicity (ADCC) potency (Patz 2011). Although it recognizes an overlapping CD20 epitope, obinutuzumab binds to CD20 in a different orientation from rituximab (Niederfellner 2011). These differentiating mechanistic features might explain its superior *in vitro* efficacy, including stronger induction of direct cell death and greater ADCC, when compared to rituximab (Mossner 2010). In accordance with these non-clinical findings, obinutuzumab has shown impressive single agent activity in a variety of advanced B cell malignancies, including CLL (Salles 2012; Sehn 2012; Morschhauser 2009). The combination of chlorambucil and obinutuzumab has shown greater first line efficacy than the combination of chlorambucil and rituximab in the first line treatment of CLL. Obinutuzmab is therefore considered to be an appropriate agent with which to combine ibrutinib in the current trial.

Ibrutinib has been used in combination with two anti-CD20 antibodies, ofatumumab and rituximab, in two phase1/2 trials CLL studies (Jaglowski 2014, Burger 2013b). Ibrutinib use in this setting was shown to be well tolerated and produced high rates of overall response (83-95%) with minimal treatment related lymphocytosis suggesting that an ibrutinib plus anti-CD20 antibody strategy is likely to be administered safely and potentially produce improved quality of responses in CLL. By combining ibrutinib with obinutuzumab, the study will be able to examine the role of ibrutinib in the first line management of CLL, when used in conjunction with what appears to be an improved anti-CD20 antibody in CLL, at least for certain patient populations such as those defined by this study.

3.2.2. Dose Selection Rationale for Ibrutinib

Ibrutinib 420 mg once daily is the regimen approved by the FDA for use in patients with CLL who have received at least one prior line of therapy (IMBRUVICA® Prescribing Information).

3.2.3. Dose Selection Rationale for Obinutuzumab

The obinutuzumab regimen of 1000 mg, given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only of Cycles 2-6 will be used in combination with ibrutinib. This is the same obinutuzumab regimen as approved in the US and used in the CLL11 trial of obinutuzumab and chlorambucil and is therefore considered the most appropriate regimen for an obinutuzumab and ibrutinib combination.

3.2.4. Selection Rationale for Comparison Arm of Chlorambucil and Obinutuzumab

The combination of chlorambucil and obinutuzumab has recently been evaluated in the front line setting in CLL patients with ongoing co-morbidity, in a comparison with either chlorambucil alone, or to the combination of chlorambucil and rituximab (Goede 2014). A total of 781 patients were randomized into the trial, with a median age of 73 years, a median creatinine clearance of 62 mL/min and a median CIRS score of 8 at baseline. Median PFS was 26.7 months for chlorambucil and obinutuzumab versus 11.1 months for chlorambucil alone. Whilst median PFS values were not reported for patients with del 17p alone, for all patients the PFS hazard ratio was 0.19 (95% CI, 0.14-0.25), in favor of the chlorambucil and obinutuzumab combination, whilst for the group with del 17p, the corresponding hazard ratio was 0.42 (95% CI, 0.17-1.04).

From the results of this study, it is clear that in a cytogenetically unselected population with extensive co-morbidities, the combination of chlorambucil and obinutuzumab offers improved disease control, when compared to chlorambucil and rituximab, with a better complete response rate (20.7% vs 7%), higher proportion of responders with MRD (46% vs 19%) and a PFS of almost 27 months versus 16 months (95% CI, 0.31 to 0.49; P<0.001). It can therefore be considered as a suitable comparator arm for the current study, in particular this regimen represents the one of the most effective available therapy options for patients who are older, or those with co-morbidities.

3.2.5. Dose Selection Rationale for Chlorambucil and Obinutuzumab

The obinutuzumab regimen of 1000 mg, given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only of Cycles 2-6 will be used in combination with chlorambucil administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle l. This is the same regimen as used in the CLL-11 trial of obinutuzumab and chlorambucil and hence considered most appropriate for the current trial.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

Disease Related

1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008).
2. Age 65 yrs and older OR if less than 65 years old, must have at least one of the following criteria:
   a. Cumulative Illness Rating Score (CIRS) >6.
   b. Creatinine clearance estimated <70 mL/min using the Cockcroft-Gault equation.
   c. Del 17p by FISH or TP53 mutation by PCR or Next Generation Sequencing (NGS).
3. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:

a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/μL).

b. Massive (≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly.

c. Massive nodes (at least 10 cm longest diameter), or progressive or symptomatic lymphadenopathy.

d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of <6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of <30,000/μL, LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.

e. Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy (see Exclusion Criteria 4).

- Autoimmune hemolytic anemia is defined by at least one marker of hemolysis (indirect bilirubin above the upper limit of normal (ULN) not due to liver disease, increased lactate dehydrogenase (above ULN) without alternative etiology, or increased absolute reticulocytosis (above ULN) or bone marrow erythropoiesis in the absence of bleeding) AND at least one marker of direct or indirect autoimmune mechanism (positive direct antiglobulin for IgG or C3d, cold agglutinins) (Ding 2007).
- Immune thrombocytopenia is defined by platelets ≤100,000/μL and increased megakaryocytes on the bone marrow exam.

f. Constitutional symptoms, defined as one or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization:

- unintentional weight loss >10% within 6 months prior to Screening.
- significant fatigue (inability to work or perform usual activities).
- fevers >100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection.
- night sweats for more than 1 month prior to Screening without evidence of infection.

4. Measurable nodal disease by computed tomography (CT), defined as at least 1 lymph node > 1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended.

Laboratory

5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to Screening and randomization:

a. Absolute neutrophil count ≥1.0 x 10^9/L.

b. Platelet count >50 x 10^9/L.

6. Adequate hepatic and renal function defined as:

a. Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN).

b. Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault).

c. Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, such as hemolysis).

Demographic

7. Men and women ≥18 years of age.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Ethical/Other

9. Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study

10. Ability to provide written informed consent and to understand and comply with the requirements of the study

11. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; 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.

12. 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 90 days after the last dose of ibrutinib/chlorambucil or obinutuzumab, and at least 18 months after the last obinutuzumab dose for female subjects.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

1. Any prior chemotherapy, radiotherapy, small molecule inhibitors including kinase inhibitors, and/or monoclonal antibody used for treatment of CLL or SLL

2. Evidence of CNS involvement with primary disease of CLL/SLL

3. History of other malignancies, except:

a. Malignancy treated with curative intent and with no known active disease present for ≥3 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 current evidence of disease.

4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura, such as those subjects with a declining hemoglobin level or platelet count secondary to autoimmune destruction within the 4 weeks prior to first dose of study drug, or the need for daily prednisone ≥20 mg daily (or corticosteroid equivalent) to control the autoimmune disease.
5. Known or suspected history of Richter's transformation.
6. Concurrent administration of >20 mg/day of prednisone within 7 days of randomization unless indicated for prophylaxis or management of allergic reactions (eg, contrast).
7. Known hypersensitivity to one or more study drugs.
8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
9. Any uncontrolled active systemic infection or an infection requiring systemic treatment that was completed ≤7 days before randomization.
10. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
11. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
12. Known history of human immunodeficiency virus (HIV) or active with hepatitis B virus (HBV) or hepatitis C virus (HCV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
13. Major surgery within 4 weeks of first dose of study drug.
14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
15. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
16. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
17. Concomitant use of warfarin or other Vitamin K antagonists.
18. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix C).
19. Lactating or pregnant.
20. Unwilling or unable to participate in all required study evaluations and procedures.

21. 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. Treatment Allocation and Blinding

This is an open-label study and no blinding will occur; neither subjects nor investigators will be blinded to treatment.

Approximately 212 subjects will be randomized. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, randomization will be stratified according to:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 vs 2
- Cytogenetics - will be stratified into one of three categories
  - del 17p
  - del 11q without del 17p
  - others (neither del 17p nor del 11q)

The randomization code will be controlled through a centralized procedure. The primary efficacy evaluation will be performed by an IRC that will be blinded to study treatment information.

5.2. Study Treatment

In all cases, treatment will be administered up to the specified maximum number of cycles, or until disease progression, unacceptable toxicity, or the subject meets any criteria specified in Section 9.2, whichever occurs first.

5.2.1. Arm A: Ibrutinib PO and Obinutuzumab IV

Ibrutinib will be given orally at a dose of 420 mg daily (3 capsules). There is no prospective limitation to the duration of ibrutinib therapy, and should be administered until progression or unacceptable toxicity.

The first dose of ibrutinib will be taken in the clinic, after which ibrutinib will be issued to the subject as an ongoing 28-day supply for home administration. On Day 1, ibrutinib will be given as soon as the subject comes into clinic. Pre-medications and obinutuzumab will then be given as outlined below.

Obinutuzumab will be administered intravenous at a fixed dose of 1000 mg over 6 cycles: given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), Day 8 (1000 mg) and Day 15 (1000 mg) of Cycle 1 and on Day 1 (1000 mg) only of subsequent cycles, for up to **6** cycles.

Intravenous obinutuzumab will be administered per Section 5.3.2.3.

In the event of permanent discontinuation of concomitant obinutuzumab therapy, treatment with ibrutinib will continue as originally scheduled.

5.2.2. Arm B: Chlorambucil PO and Obinutuzumab IV for Six 28-day Cycles

Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle. On Day 1, chlorambucil will be given as soon as the subject comes into clinic. Pre-medications and obinutuzumab will then be given as outlined below. Chlorambucil will be administered in the clinic on days which coincide with concomitant obinutuzumab (Days 1 + 15 of Cycle 1 and Day1 of Cycles 2-6) and will be issued to the subject for home administration on other occasions (Day 15 of Cycles 2-6).

For subjects who have difficulty taking the entire dose of chlorambucil at a single time, the pills may be split up into 2 to 3 batches to be taken over 8 hours on the same day. The dose should not be taken over more than one day.

Obinutuzumab will be administered intravenously at a fixed dose of 1000 mg over 6 cycles: given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 and on Day 1 only of subsequent cycles.

Intravenous obinutuzumab will be administered per Section 5.3.2.3.

In the event of permanent discontinuation of concomitant obinutuzumab therapy, treatment with chlorambucil will continue as originally scheduled.

5.3. Study Medications

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

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.

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

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day 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. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix C).

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be re-dispensed to anyone.

5.3.1.3. Overdose

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 Serious Adverse Event (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 11.4 for further information regarding AE reporting.

5.3.1.4. Dose Modification for Adverse Reactions

Treatment with ibrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity.

A hematologic AE grading scheme for hematologic toxicity is included in Appendix D.

The dose of study drug must be modified according to the dose modification guidance in Table 1 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC<500/μL) for more than 7 days. See Section 6.1 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets<50,000/μL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (platelets<25,000/μL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

A high number of circulating malignant cells (>400,000/μL) may confer increased risk; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

Table 1: Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day for 420 mg/day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 140 mg/day for 420 mg/day dose)
Fourth	Discontinue study drug

Study treatment interruptions, dose reductions or modifications, or any other changes in study drug administration should be recorded in the clinical database. Study treatment should be discontinued in the event of an ibrutinib toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Study drug should be re-started as soon as clinically appropriate.

After a dose reduction, dose escalations of ibrutinib to the previous higher dose may be considered after consultation with the Medical Monitor if the event does not recur after at least one cycle of the lower dose.

For required dose modification for hepatic impairment refer to Section 5.3.1.6 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.

5.3.1.5. Leukocytosis/Leukostasis

A high number of circulating malignant cells (>400,000/μL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as

hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

5.3.1.6. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of Screening (Child- Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo 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 J).

5.3.2. Obinutuzumab

Refer to the obinutuzumab Investigator's Brochure for additional information.

5.3.2.1. Formulation/Packaging/Storage

Obinutuzumab is manufactured by Roche/Genentech, a member of the Roche Group, and is supplied as 1000 mg/40 mL (25 mg/mL) single-use vials containing preservative-free solution (NDC 50242-070-01) are stable at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. Obinutuzumab vials should be protected from light. DO NOT FREEZE. DO NOT SHAKE.

For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C (36°F to 46°F) followed by 48 hours (including infusion time) at room temperature (≤ 30°C/86°F). Obinutuzumab does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2–8°C. No incompatibilities between obinutuzumab and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Obinutuzumab with 0.9% sodium chloride.

5.3.2.2. Premedication

All subjects should be premedicated with acetaminophen/paracetamol to reduce the risk of obinutuzumab related infusion reactions, as detailed in Table 2 below.

Subjects with a history of cardiac disease should be monitored closely. In addition these subjects should be hydrated with caution in order to prevent a potential fluid overload. Hypotension may occur during obinutuzumab administration. Consider withholding antihypertensive treatments for

12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.

Table 2: Premedication to be Administered Before Obinutuzumab Infusion to Reduce the Risk of Infusion Related Reactions (Mandatory for CLL Subjects Receiving the First Dose)

Day of Treatment Cycle	Subjects requiring premedication	Premedication	Administration
Cycle 1: Day 1	All subjects	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histaminic drug[3]	
Cycle 1: Day 2	All subjects	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histaminic drug[3]	
Cycle 1: Day 8, Day 15	Subjects with a Grade 3 IRR with the previous infusion OR subjects with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
Cycles 2-6: Day 1	All subjects	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
	Subjects with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic drug[3]	

1. 20 mg dexamethasone or 80 mg methylprednisolone or equivalent given intravenously. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
2. eg, 1000 mg acetaminophen/paracetamol
3. eg, 50 mg diphenhydramine

Tumor Lysis Syndrome (TLS)

Subjects with a high tumor burden (white blood cell count ≥25 x 10^9/L or bulky lymphadenopathy) must receive prophylaxis for TLS prior to the initiation of treatment (McBride and Westervelt 2012). This includes appropriate hydration, consisting of a fluid intake of approximately 3 liters per day, starting 1–2 days before the first dose of obinutuzumab. All such subjects with high tumor burden must be treated with allopurinol or a suitable alternative treatment (ie, rasburicase) starting at least 72 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). These measures may also be extended to other subjects considered at risk of TLS in the judgment of the investigator.

Subjects still considered at risk for TLS because of persistently high tumor burden (ie, peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (ie, rasburicase) and adequate hydration until the risk is abated, as determined by the investigator.

All subjects considered at risk by the investigator should be carefully monitored during the initial days of study treatment with a special focus on renal function, potassium, and uric acid values.

Any additional guidelines should be followed according to institutional practice (McBride and Westervelt 2012).

Neutropenia

Subjects with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

5.3.2.3. Dosage Regimen and Administration

Obinutuzumab should be diluted in 0.9% Sodium Chloride Injection, USP or local equivalent. Do not use other diluents, such as 5% Dextrose in Water. Do not co-administer or mix obinutuzumab with any other intravenous drug.

Each dose of obinutuzumab is 1000 mg, with the exception of the first infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg) (Gazyva USPI 2013). Obinutuzumab should be administered as an IV infusion, according to the following schedule:

Table 3: Obinutuzumab Dosing Schedule

Day of Treatment Cycle		Dose of Obinutuzumab	Rate of infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate
	Day 2	900 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycle 2-6	Day 1	1000 mg	

If a subject experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if subject does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if subject experience a Grade 3 infusion related symptom at re-challenge.
- Grade 1–2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if subject does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

5.3.2.4. Dose Delay

Treatment with obinutuzumab should be held for any unmanageable, potentially obinutuzumab-related toxicity which merits a dose delay, in the opinion of the investigator. In particular, this includes subjects experiencing an infection, Grade 3 or 4 cytopenia (according to Grading Scale for hematologic toxicities in CLL studies, Appendix D), or a Grade ≥2 non-hematologic toxicity. In principle, obinutuzumab therapy should be withheld until toxicity has resolved to at least Grade 1. In certain circumstances, therapy with obinutuzumab may be re-initiated despite an ongoing toxicity which has not resolved to Grade ≤1, providing it is clinically appropriate to do so, in the opinion of the investigator and that this has been discussed first with the Medical Monitor.

Obinutuzumab should be discontinued if progressive multifocal leukoencephalopathy (PML) is suspected.

Any other clinically important events where dose delays may be considered appropriate by the investigator should be discussed with the Medical Monitor.

Obinutuzumab may be held for a maximum of 28 days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the Medical Monitor.

5.3.2.5. Obinutuzumab Dose Modifications

Thrombocytopenia

Severe and life-threatening thrombocytopenia has been observed during treatment with obinutuzumab. In CLL patients exposed to chlorambucil and obinutuzumab, fatal hemorrhagic

events have been reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established.

Subjects should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (ie, platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Toxicity	Obinutuzumab
Severe thrombocytopenia (platelets <10,000/µL) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet inhibitors	• Hold obinutuzumab in case of severe thrombocytopenia (platelets <10,000/µL) or symptomatic bleeding (irrespective of platelet count) until it resolves. If Cycle 1 Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved). • If Cycle 1 Day 15 is delayed then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab as scheduled (if symptomatic bleeding has resolved).
Thrombocytopenia with platelets <20,000/µL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors	• Hold obinutuzumab in case of platelets <20,000/µL or symptomatic bleeding (irrespective of platelet count) until it resolves. If Cycle 1 Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab as scheduled (if symptomatic bleeding has resolved). • At the discretion of the study investigator, for patients who are on LMWH, when thrombocytopenia with platelets <20,000/µL develops, reduce the dose of LMWH used. • At the discretion of the study investigator, for patients who are on platelet inhibitors, when thrombocytopenia with platelets <20,000/µL develops, consideration should be given to temporarily pause their use

If the clinical condition of subject requires the use of concomitant anticoagulants, the subjects are at increased risk of bleeding when thrombocytopenia with platelets <20,000/µL develops.

While subjects are on both ibrutinib and obinutuzumab, dose modification / hold for each individual study drug should follow criteria set forth under that drug.

While subjects are on both chlorambucil and obinutuzumab, dose modification / hold for each individual study drug should follow criteria set forth under that drug.

5.3.2.6. Continuation of Obinutuzumab in the Event of Discontinuation of Concomitant Ibrutinib/Chlorambucil

In the event of permanent discontinuation of concomitant ibrutinib (Arm A) or chlorambucil (Arm B) for any reason, treatment with obinutuzumab will be continued to complete a total of 6 cycles of therapy with obinutuzumab.

5.3.3. Chlorambucil

5.3.3.1. Formulation/Packaging/Storage

Chlorambucil (LEUKERAN®) is manufactured by Aspen and is supplied as brown, biconvex tablets containing 2 mg chlorambucil in amber glass bottles with child-resistant closures. The recommended storage condition for chlorambucil tablets is in a refrigerator, 2° to 8°C (36° to 46°F).

5.3.3.2. Dosage and Administration

Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle. On Day 1, chlorambucil will be given as soon as the subject comes into clinic. Pre-medications and obinutuzumab will then be given as outlined in Table 2.

Chlorambucil will be administered in the clinic on days which coincide with concomitant obinutuzumab (Days 1 + 15 of Cycle 1 and Day1 of Cycles 2-6) and will be issued to the subject for home administration on other occasions (Day 15 of Cycles 2-6).

For subjects who have difficulty taking the entire dose of chlorambucil at a single time, the pills may be split up into 2 to 3 batches to be taken over 8 hours on the same day. The dose should not be taken over more than one day.

Unused chlorambucil dispensed during the previous visit must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned tablets must not be re-dispensed to anyone.

5.3.3.3. Dose Delay and Modifications

Treatment with chlorambucil should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Chlorambucil may be held for toxicity up to a maximum of 28 consecutive days, after which it should be discontinued, unless reviewed and approved by the Medical Monitor. Guidelines for dose modifications are outlined in Table 4 due to AE irrespective of causality. At the investigator's discretion, a subject's dose may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

If institutional guidelines for chlorambucil dose modifications are different from these guidelines, variances will be permitted after discussion with the Medical Monitor.

Table 4: Dose Modifications for Chlorambucil Due to Toxicity

Toxicity	Chlorambucil Dose Action
ANC <500/μL for >7 days	Hold until recovery to >1,000/μL; restart at a 25% decrement of the original dose and at each occurrence
Platelets <50,000/μL with bleeding	Hold until recovery to >50,000/μL and resolution of bleeding; restart at full dose
Platelets <25,000/μL with or without bleeding (ongoing or at any time during previous cycle)	Hold until recovery to >50,000/μL and resolution of bleeding; restart at a 25% decrement of the original dose and at each occurrence
Unmanageable Grade 3 nonhematologic toxicity	Hold until recovery to Grade ≤1 or baseline; restart at original dose
Grade 4 nonhematologic toxicity (ongoing or at any time during previous cycle)	Hold until recovery to Grade ≤1 or baseline; restart at a 25% decrement of the original dose and at each occurrence
Repetitive or intractable Grade 3/4 nonhematologic toxicity or any Grade 4 toxicity deemed related to study drug	Discontinue study drug

5.3.3.4. Warnings, Precautions, and Adverse Effects

Common chlorambucil-related toxicities tend to be hematologic: neutropenia, anemia, and thrombocytopenia. Refer to the current chlorambucil package insert for warnings, precautions, and additional adverse effects.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of study drug.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006) except as outlined in Section 6.3 below. Transfusions may be given in accordance with institutional policy.

Corticosteroids at dosages equivalent to prednisone >20 mg/day administered consecutively for >14 days are not allowed.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, cobicistat, or posaconazole) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).
- No dose adjustment is required in combination with mild inhibitors.

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

A list of common CYP3A inhibitors and inducers is provided in Appendix C. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.2.2. 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. 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.

6.2.3. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4).

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

6.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

After consultation with the medical monitor the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Erythropoietic growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and sargramostim are also prohibited for the first 6 months of study treatment. However, initiation of erythropoietic growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and/or sargramostim can be considered after 6 months on study based on the indication outlined in the respective package inserts. Corticosteroids for the treatment of the underlying disease are prohibited. Please refer to Section 6.1 for corticosteroid use in other medical situations.

6.4. 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:

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], 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.

6.4.2. Major Surgical Procedures

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.

6.4.3. Emergency Procedures

For emergency procedures, ibrutinib should be held as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

7.1.1.1. ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific Screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA) or applicable country regulation. In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria prior to randomization (Section 4).

7.1.1.3. Medical History and Demographics

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.

7.1.1.4. Prior and Concomitant Medications

All medications from the signing of ICF through 30 days after the last dose of study drug will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until death, subject withdrawal of full consent, loss to follow-up, or study termination by Sponsor, whichever comes first.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition must be recorded from the time the ICF is signed until 30 days after the last dose of study drug. Laboratory abnormalities designated

clinically significant by the Investigator will also be recorded as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.4.

7.1.1.6. Physical Examination

The physical examination will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side.

A limited symptom-directed physical examination is required at Cycle 1 Days 8 and 15 visits.

7.1.1.7. Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms at Screening and with all subsequent physical exams while on treatment.

If there are any eye-related symptoms of severity Grade ≥2 at Screening or if the subjects develop any eye-related symptoms of severity Grade ≥2 while on study treatment, an ophthalmologic evaluation/consult must be performed and the outcome must be reported on the ophthalmologic eCRF.

7.1.1.8. ECOG

The ECOG performance index is provided in Appendix B.

7.1.1.9. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

7.1.1.10. Patient-Reported Outcomes

The PRO instrument, EQ-5D-5L (Appendix E), will be administered in this study. These questionnaires are to be completed by the subject prior to any other study procedures at that visit.

The EQ-5D-5L is a standardized instrument used to measure of health outcome (EuroQol Group 1990) and consists of a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 dimensions are used to compute a single utility score ranging from 0 to 1, representing the general health status of the individual. The 5 dimensions evaluated are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

7.1.1.11. Cumulative Illness Rating Scale (CIRS)

The CIRS is a measure of comorbid medical conditions. As an individual ages, the number of comorbid medical conditions increases, which can impact treatment tolerance to anti-cancer therapy (Welch 1996). The scoring sheet for CIRS is found in Appendix F.

7.1.1.12. Medical Resources Usage (MRU)

Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected for each treatment arm.

7.1.1.13. Study Drug Compliance Review

Study drug compliance review includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration.

7.1.2. Laboratory

7.1.2.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. Creatinine clearance (Cockroft-Gault) will be calculated with every serum chemistry.

7.1.2.3. Coagulation Panel

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening.

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C antibody, and will be evaluated by central laboratory. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative PCR result before enrollment. Those who are PCR positive will be excluded.

7.1.2.5. Pregnancy Test

Serum pregnancy test will be performed centrally at Screening only for women of reproductive potential. A urine pregnancy test will also be performed on Day 1 prior to first dose. 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.

7.1.3. Diagnostics/Procedures

7.1.3.1. ECG

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, 12-lead ECGs will be done *in triplicate* (≥1 minute apart).

Abnormalities noted at Screening should be included in the medical history.

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

7.1.3.2. CT/MRI

CT scans of the neck, chest, abdomen and pelvis will be performed throughout the study until disease progression is confirmed. MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). If MRI is required for any other reason, this must first be discussed with the study medical monitor.

7.1.3.3. Bone Marrow Aspirate And Biopsy

Bone marrow samples will be used for minimal residual disease assessment, to confirm cytopenic progression and distinguish autoimmune and treatment-related cytopenias.

For Screening

A unilateral bone marrow aspirate or biopsy must be obtained at Screening or up to 90 days prior to randomization.

For Response Evaluation

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters, a bone marrow aspirate and biopsy must be obtained to confirm the CR and to evaluate minimal residual disease

(MRD). In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias.

For Evaluation of Clonal Evolution

A bone marrow sample should also be collected at the time of disease progression for examination of clonal evolution (acquisition of new cytogenetic abnormalities defined as new del 11q, del 17p, or trisomy 12 by FISH, or other cytogenetic abnormalities).

For Assessment of Minimal Residual Disease (MRD)A peripheral blood and bone marrow aspirate will be collected from all subjects at Cycle 9 and in those with a suspected CR after the start of study treatment, for assessment of MRD status.

- All responders who have an MRD-negative status in the bone marrow, should be followed with peripheral blood MRD assessments every 4 cycles until Cycle 33 then every 6 cycles starting at Cycle 39.
- All responders who have an MRD-positive status in the bone marrow or peripheral blood, should also be followed with peripheral blood MRD assessments every 4 cycles until Cycle 33 then every 6 cycles starting at Cycle 39. Once the subject becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.
- A bone marrow aspirate will not be required at Cycle 9 for subjects who have unequivocal evidence of ongoing gross clinically detectable disease (eg, lymph node >2 cm), however these subjects should have a peripheral blood sample sent for MRD analysis and a bone marrow aspirate should be considered for the next scheduled response assessment visit.

The following material will be sent to the central laboratory:

- Bone marrow trephine (≥1 cm) in a container of neutral buffered formalin (no other fixative allowed);
- Bone marrow aspirate
- Peripheral blood for MRD analysis.

7.1.3.4. Cytogenetics: FISH / TP53 Assays

Cytogenetic profiles will use FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p. TP53 mutational status will be measured. For subjects with unknown del 17p or del 11q or TP53 status, a peripheral blood or bone marrow sample (aspirate or biopsy) must be tested, in accordance with institutional policies and procedures within 180 days prior to randomization. For subjects without lymphocytosis at Screening, FISH and/or TP53 assessment should be performed on the bone marrow sample.

Existing FISH and TP53 results performed within the last 180 days prior to randomization, confirming the status of del 17p, del 11q and TP53 as per the assay specification will be

considered adequate for eligibility and stratification purposes, provided appropriate documentation is available.

For all subjects, screening peripheral blood (required) and marrow samples (where available) will be sent to the designated central laboratory to be tested for 17p-, 13q-, +12, and 11q-.

7.1.3.5. Genetic and Molecular Prognostic Markers

A blood sample will be collected from all subjects during Screening and analyzed centrally to examine pretreatment prognostic factors.

These will include immunoglobulin heavy-chain variable (IgVH) and other genes known to be involved in CLL prognosis (eg, TP53, and Notch 1, SF3B1) mutational status.

In addition, genomic profiling of the tumor cells may be performed at baseline, during treatment or at progression as needed.

7.1.4. Pharmacokinetics/Biomarkers

7.1.4.1. Sparse Pharmacokinetics

Sparse PK samples will be collected in all subjects randomized to receive ibrutinib. The samples will be collected per subject as described below:

Cycle 1, Day 15:

1. Pre-dose
2. 1 hour (window: 45–75 minutes)
3. 2 hours (window: 1.5–2.5 hours)
4. 4 hours (window: 3.5–4.5 hours)

Cycle 2, Day 1:

1. Pre-dose (30-60 minutes before the dose)

Refer to the laboratory manual for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to 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. In the event that medical management (use of steroids) is needed, use of steroids for infusion should be recorded.

7.1.4.2. Biomarker Assays

Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib will be explored in this study.

For all subjects a predose blood sample will be collected at the specified visits per the Schedule of Assessments (Appendix A). If a subject progresses and returns to clinic within 24 hours after his or her last dose of ibrutinib, then an additional post-progression blood sample will be collected. If this post-progression blood sample is collected, then the biomarker blood sample collection at the EOT Visit is not required.

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, pharmacodynamic, biomarker and pharmacogenomic assessments.

A portion of pre-treatment bone marrow samples collected may be used by Sponsor for further biomarker analysis.

7.1.4.3. Flow Cytometry-based Whole Blood Assays

To explore and determine the temporal effect of drug combinations on the phenotype of the tumor cells and the immune system, blood samples will be collected on Day 1 of Cycle 1 (baseline), and at the intervals indicated in Section 8. Samples will also be collected at a suspected CR and at disease progression or discontinuation of treatment. Possible analyses will include but not limited to the staining for subpopulations of T, B, and NK cells.

7.1.4.4. Cytokine and Chemokine Levels during Infusion of Obinutuzumab

To explore and evaluate the impact of ibrutinib/chlorambucil on obinutuzumab-related infusion reactions, plasma will be collected at pre-dose ibrutinib/chlorambucil, immediately prior to infusion of obinutuzumab, and 2 and 4 hours into the obinutuzumab infusion for a total of 4 time points on Day 1. The samples will be evaluated for secreted proteins related to infusion reactions, such as IL-6, TNF-alpha, as well as other cytokines and chemokines.

7.2. Main Efficacy Evaluations

Disease evaluations will include:

- Physical examination (which will focus on the presence/absence of size increase/ decrease in lymph nodes, liver, and spleen)
- Hematologic parameters by CBC performed at a central laboratory
- Radiographic evaluation (CT or MRI scan of the neck, chest, abdomen, and pelvis)

- Bone marrow aspirate and/or biopsy at Cycle 9 and as appropriate if there is evidence of CR in the other response parameters.
- MRD evaluation for subjects as described in Section 7.1.3.3.

If study drug is held before a scheduled response assessment then the response assessment can be delayed up to 4 weeks to allow re-initiation of study drug for 2 weeks (or as long as possible) prior to performing scheduled response assessment.

Efficacy assessments, for the purpose of the study result analyses, will be performed by an IRC blinded to study treatment information and independent of Investigators and personnel who are involved in the conduct of the study. The process and convention of the IRC will be detailed in a separate charter.

7.2.1. Definitions

7.2.1.1. Refractory

Refractory is defined as treatment failure or progression within 12 months post-treatment.

7.2.1.2. Relapsed

Relapsed is defined as a subject who met criteria for CR or PR, but progressed beyond 12 months post-treatment.

7.2.1.3. Treatment Failure

Treatment failure is defined as best response of progressive disease or SD while on study treatment.

7.2.1.4. Measurable Disease

Subjects must have at least 1 measurable site of disease to participate in this study. Measurable sites of disease are defined as lymph nodes, or lymph node masses. Each measurable site of disease must be greater than 1.5 cm in the longest diameter. Measurement must be determined by imaging evaluation.

Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If there are tumor lesions in previously irradiated areas and progression has occurred, these lesions will be considered measurable. If tumor lesions in previously irradiated areas are present and have been stable, then these lesions are not considered measurable. If tumor lesions in previously irradiated areas progress during the study, then disease progression will be considered as having occurred provided progression is confirmed by IRC.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures, as necessary, including peripheral blood counts.

7.2.1.5. Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline and ≥5000/μL that occurs in the setting of unequivocal improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hgb or platelet count), or disease-related symptoms. Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent pharmacodynamic phenomenon observed with initiation (or re-initiation) of ibrutinib.

Response assessment in CLL subjects treated with novel agents has been clarified by the authors of the IWCLL 2008 guidelines and is outlined in the NCCN NHL 2012 guidelines, supporting that subjects with isolated lymphocytosis in the setting of improvement in other disease parameters should not be considered to have progressive disease or treatment failure (Cheson 2012).

7.2.1.6. Richter's Transformation

Richter's syndrome (RS) is lymphomatous transformation to a more aggressive histology in a subject with CLL or SLL. RS is most often characterized by the development of high-grade NHL or Hodgkin's disease. Symptoms of Richter's transformation can include new or progressive lymphadenopathy or organomegaly, fever, loss of weight and muscle mass, and other health problems. Richter's transformation can be suggested by a CT/PET scan, but should be confirmed with a biopsy (eg, lymph node) demonstrating the histologic transformation.

7.2.1.7. Minimal Residual Disease (MRD)

Subjects who have achieved a CR/CRi should be evaluated for eradication of disease cells as determined on both peripheral blood and bone marrow aspiration. Subjects with a PR/nPR should be evaluated for MRD using a peripheral blood sample (or a bone marrow aspirate if possible) once MRD is confirmed negative in the peripheral blood a bone marrow aspirate must be sent to confirm MRD negativity at next clinical assessment. MRD negativity is defined as <1 CLL cell per 10,000 leukocytes.

7.2.2. Guidelines for Disease Evaluation

Table 5 outlines what is required for each parameter at baseline to be evaluable throughout the study.

Table 5: Evaluable Parameter Requirements

Parameter	Requirements to be Evaluable for Response
Measurable Disease (required for all subjects)	Lymph Node > 1.5cm
Splenomegaly	Enlarged spleen
Hepatomegaly	Enlarged liver
Absolute Lymphocyte Count (ALC)	≥ 4,000 /μL
Platelets	≤100,000 /μL
Absolute Neutrophil Count (ANC)	≤ 1500 /μL
Hgb	≤ 11.0 g/dL

7.2.3. Response Categories

Assessment of response should include physical examination, radiographic imaging, and evaluation of blood and marrow (if applicable). Definition of response for CR, CRi, nPR, PR, and disease progression will be evaluated by the criteria listed in Table 6. Group A criteria define the tumor load and Group B criteria define the function of the hematopoietic system. Response must be confirmed by CT and central labs, and must last at least 2 months without transfusional support or growth factor product to be considered a confirmed response.

Table 6: Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None; ≤1.5cm	Decrease ≥50%	increase ≥50%
Hepatomegaly	None	Decrease ≥50%	increase ≥50% or new hepatomegaly
Splenomegaly	None	Decrease ≥50%	increase ≥50% or new splenomegaly
Blood lymphocytes	<4000/μL	Decrease ≥50% from baseline	increase ≥50% over baseline[c]
Marrow[b]	Normocellular, <30% lymphocytes, no B lymphoid nodules. Hypocellular defines CRi		
Group B			
Platelet count	>100,000/μL	>100,000/μL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils	>1500/μL	>1500/μL or increase ≥50% over baseline	N/A

[a] Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node

[b] This parameter is not relevant for the PD category unless confirming cytopenic progression.

[c] Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease (see Section 7.2.1.5). For subjects without treatment-related lymphocytosis, PD by lymphocyte count can be considered based on ≥50% increase from the nadir count if confirmed by central lab on ≥2 serial assessments if the ALC is ≥30,000/μL and lymphocyte doubling time is rapid.

Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system

CR: all of the criteria need to be met and subjects have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.

PR: At least two of the Group A parameters must be met; with two exceptions: 1) subjects who only have abnormal lymph nodes at baseline, or 2) subjects who have only abnormal lymph node and abnormal lymphocyte count (ALC) at baseline. For these two exceptions, subjects will only need to meet the lymph node response criteria.

In addition to the Group A criteria, all subjects must also have a response in at least one of the Group B criteria.

SD: the absence of PD and the failure to achieve a response.

PD: at least 1 of the above criteria from Group A or B are met or development of transformation to a more aggressive histology

Cross reference: Hallek 2008, Hallek et al. June 2012 e-letter, Hallek 2013

7.2.3.1. Complete Response (CR)

All of the following are required for a CR:

- No significant lymphadenopathy (>1.5cm) palpable on examination or by CT
- No hepatosplenomegaly on examination or by CT
- No constitutional symptoms (ie, no fever >38°C for ≥2 weeks, no unintentional ≥10% body weight loss within last 6 months, no night sweats for >1 month without other evidence of infection, no fatigue interfering with work or usual activities)
- Neutrophils >1.5 x10^9/L, platelets >100,000/μL, and Hgb >11g/dL without recent growth factor or transfusions
- ALC <4,000 /μL

Marrow aspirate and biopsy must be performed by local lab after all other criteria meet the definition of CR. To define a CR, the marrow sample should be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. B-lymphoid nodules should be absent. In addition, in subjects with a CR, MRD should be performed on both peripheral blood and bone marrow aspirate to evaluate MRD status.

7.2.3.2. Complete Response with an Incomplete Marrow Recovery (CRi)

CRi is defined as a CR with an incomplete recovery of the subject's bone marrow. Subjects who have a CRi fulfill all criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia. These cytopenias are due to drug toxicity in the bone marrow and are not due to any evidence of CLL.

7.2.3.3. Nodular Partial Response (nPR)

nPR is a response where subjects meet criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules, which may represent a clonal infiltrate. These nodules are residual disease and therefore the subject is termed an nPR.

7.2.3.4. Partial Response (PR)

At least two of the following parameters must be met; with two exceptions: 1) subjects who only have abnormal lymph nodes at baseline, or 2) subjects who have only abnormal lymph node and abnormal lymphocyte count (ALC) at baseline. For these two exceptions, subjects will only need to meet the lymph node response criteria.

- ≥50% decrease in the sum products of up to 6 lymph nodes, a ≥50% decrease in the longest diameter of the single lymph node, or normalization of lymphadenopathy when compared to baseline.

- With no new enlarged lymph nodes by physical examination or CT AND no increase in any lymph node by CT. Note: In a small lymph node <2 cm, an increase of less than 25% is not considered to be significant.

- When abnormal, a ≥50% decrease in the enlargement of the spleen and/or liver from baseline or normalization by CT
- If abnormal a ≥50% drop in lymphocyte count from baseline or ≤4.0 x 10^9/L

In addition to the criteria above, the subject must also have a response in at least one of the following evaluable criteria independent of growth factor support or transfusion.

- Neutrophils >1.5 x10^9/L or ≥50% improvement over baseline
- Platelets >100,000/μL or ≥50% improvement over baseline
- Hgb >11 g/dL or ≥50% improvement over baseline

* Note: If all criteria are normal, defined as neutrophils >1.5 x10^9/L, platelets >100,000/μL, and Hgb >11g/dL at baseline, they must remain normal to be considered consistent with a PR.

7.2.3.5. Stable Disease (SD)

Not meeting criteria for CR, CRi, nPR, PR, or progressive disease.

7.2.3.6. Progressive Disease

A CT scan is required to evaluate all cases of suspected progressive disease for this protocol regardless of the modality of disease progression (eg, lymph node, lymphocytosis, or transformation). Progressive disease requires at least ONE of following:

- New enlarged nodes >1.5cm, new hepatomegaly or splenomegaly; or other organ infiltrates
- ≥50% increase from nadir in existing lymph node (must reach >1.5 cm in the longest diameter) or ≥50% increase from nadir in sum of product of diameters of multiple nodes
- ≥50% increase from nadir in enlargement of liver or spleen
- ≥50% increase from the nadir count if confirmed by central lab on ≥2 serial assessments if the ALC is ≥30,000/μL and lymphocyte doubling time is rapid, unless considered treatment related lymphocytosis (Section 7.2.1.5)
- New cytopenia (Hgb or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia, drugs, or bleeding), as documented by a decrease of Hgb levels from baseline by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL) and lower than baseline, or by a decrease of platelet counts from baseline by ≥50% or to less than 100 × 10^9/L (100,000/μL) and lower than baseline in the presence of active CLL, defines disease progression ; a marrow biopsy must demonstrate an infiltrate of clonal CLL cells if no other evidence of disease progression is present on CT scan.
- Transformation to a more aggressive histology (eg, Richter's Transformation). Whenever possible, this diagnosis should be established by biopsy.

Suspected progressive disease must be confirmed by a serial exam at least 2 weeks later. Please see Section 7.2.6 on details regarding suspected PD and IRC confirmation.

7.2.4. Hematological Improvement

In all subjects and the subset of subjects with cytopenia(s) at baseline (Hgb ≤11 g/dL, platelets ≤100,000/μL), time to improvement in blood counts and percentage of subjects with improvement at Cycle 9 Day 1 response assessment and the percentage with improvement in blood counts (sustained improvement, defined as improvement in cytopenia by an increase of Hgb levels from baseline by ≥2 g/dL, or an increase of platelet counts from baseline by ≥50%, with the duration of improvement lasting for at least 56 days without blood transfusion or growth factors) will be recorded.

7.2.5. Radiographic Images Assessment

Radiological efficacy assessments, for the purpose of the study result analyses, will be performed by the IRC, which will be blinded to study treatment information. The process and convention of the review will be detailed in a separate charter.

The baseline disease assessment will include all areas of known and suspected disease with use of the most appropriate and reproducible radiological technique.

Radiological imaging by CT with contrast is required and must include the neck, chest, abdomen, and pelvis. Subjects who are intolerant to IV CT contrast agents will have CT scans performed with oral contrast. When possible, all subjects should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be utilized for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given subject throughout the study as much as possible.

Magnetic resonance imaging (MRI) may be used to evaluate non-target lesions that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). If MRI is required for any other reason, this must be discussed with the study Medical Monitor first.

CT scans will be performed until disease progression regardless of whether or not the subject remains on treatment. In the event disease progression is suspected due to physical examination or laboratory test, a CT scan must be performed to confirm disease progression.

There must be radiographically measurable disease at Screening (at least one lymph node >1.5 cm in the longest diameter) as outlined in Section 7.2.2. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

Up to 6 measurable lymph nodes (target lesions >1.5 cm in the longest diameter), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study.

The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at Screening and all subsequent response evaluations, in accordance with the provisions of a separate radiology charter.

A central imaging service will be utilized to provide independent radiological assessments for the purposes of the primary endpoint. These measurements will not be reported back to the site.

7.2.6. Suspected Disease Progression

The schedule of assessments is provided in Appendix A. Any suspected case of disease progression will prompt procedures performed in a Suspected Disease Progression visit (Section 8.2.1.5). Disease progression should be confirmed with a CT scan (or MRI, if CT is contraindicated) and should be reported to the Sponsor within 24 hours of discovery. If disease progression is suspected based on the results of a single examination (including CT scan) or a single laboratory parameter, this finding should be confirmed by a subsequent evaluation at least 2 weeks later.

Study treatment should be continued and new anticancer therapy withheld, if clinically appropriate, until disease progression is confirmed by the IRC. Subjects should continue to adhere to all study-related procedures—including response evaluations and procedures to confirm disease progression—until progressive disease is confirmed by IRC. When disease progression has been confirmed by the IRC, study treatment should be discontinued.

If there is uncertainty regarding whether there is disease progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 2-4 week intervals). Transient worsening of disease during temporary interruption of study therapy (eg, for drug-related toxicity, intercurrent illness, or surgery) may not indicate disease progression.

Blood tests performed locally for determination of response or disease progression will need to be repeated by the central laboratory for confirmation of results.

7.3. Sample Collection And Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix A) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8. STUDY PROCEDURES

The study is divided into a Screening Phase, a Pre-PD Phase, and a Follow-up Phase. The Schedule of Assessments (Appendix A) summarizes the frequency and timing of efficacy, PK, biomarker, and safety measurements applicable to this study. Please note the timing of all Pre-PD Phase visits will be based on using Cycle 1 Day 1 (C1D1) as the anchor visit and all subsequent visits should use the C1D1 date as the basis for scheduling.

8.1. Screening Phase

Screening procedures will be performed up to 30 days prior to randomization, 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. All study tests and procedures should be performed at the study center at which the subject was enrolled and will be receiving treatment. After signing the ICF, and being deemed eligible for entry, subjects may be enrolled in the study.

8.1.1. Screening Visit

The following procedures will be performed at the Screening Visit within 30 days prior to randomization unless otherwise noted:

- Obtain signed, written informed consent
- Medical history including demographic information
- Perform a complete physical examination, including height and weight (may use prior height measurement if available in source documents)
- Evaluation of ECOG performance status
- Perform PRO EQ-5D-5L assessment
- Obtain vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) after the subject has rested in the sitting position
- Obtain triplicate 12 lead ECG (≥1 minute apart) after the subject has been in a supine position and resting for at least 10 minutes.
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs
- Adverse events
- Imaging by CT or other modality as described in Section 7.2.5 (if not performed within 6 weeks prior to randomization)

- Obtain a bone marrow aspirate and biopsy (if not performed within 90 days prior to randomization)
- Calculate Cumulative Illness Rating Score (CIRS) (Appendix F)
- Obtain blood specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry (including creatinine clearance)
  - Coagulation panel (PT/INR, aPTT)
  - Hepatitis serologies
  - Cytogenetics: CLL FISH panel (eg, del 17p) within 180 days of randomization, see Section 7.1.3.4)
  - Genetic/molecular prognostic factors (eg, TP53, Notch 1, SF3B1)
  - Obtain serum pregnancy test for women of reproductive potential only

8.2. Pre-progressive Disease (Pre-PD) Phase

Following completion of the Screening Visit and once eligibility has been confirmed (per inclusion/exclusion criteria), subjects will be randomized to either Treatment Arm A or Treatment Arm B via an Interactive Web Response System (IWRS) or alternative system provided by the Sponsor. Randomization should occur as close to the time of the expected first dose as possible but no later than 3 days prior to expected first dose with study drug.

For subjects randomized to Treatment Arm A, **ibrutinib** therapy should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

All **other study medications** in both Treatment Arm A and Treatment Arm B should be continued until the protocol specified number of cycles has been completed (or the occurrence of disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2 occur first). Each cycle will last for a total duration of 28 days. Local labs may be used to guide all dosing-related decisions and should be followed up with central labs. In the event of clinically suspected disease progression, the subject may continue to receive study medication, at the discretion of the Investigator, until disease progression is confirmed.

All subjects randomized to study treatment will continue following all study procedures and visits following the pre-PD schedule until disease progression is confirmed by IRC, including subjects on Arm B who complete treatment and any subjects who discontinue study treatment early.

Refer to the Schedule of Assessments (Appendix A) for a complete list of procedures to be performed at each scheduled study visit.

8.2.1. Treatment Visits

8.2.1.1. Cycle 1 Visits

Cycle 1 Day 1 (C1D1) Visit

Pre-dose

The following procedures will be performed prior to dosing (within 3 days) of the C1D1 Visit. Please note, C1D1 Visit procedures done at Screening will not need to be repeated **if done within 3 days of first dose with study drug.**

- Confirm eligibility (per inclusion/exclusion criteria) and randomize via IWRS. Dosing should occur within 3 days of randomization.
- Adverse events
- Physical examination
- Vital signs
- Perform PRO EQ-5D-5L assessment
- ECOG performance status
- Concomitant medications
- Hematology
- Serum chemistry (including creatinine clearance)
- Flow cytometry blood assays
- Biomarker assays
- Perform urine pregnancy test for women of childbearing potential only
- Infusion reaction cytokines/chemokines (prior to ibrutinib/chlorambucil dosing)

Dosing

- Administration of study medication (oral study drug is given prior to obinutuzumab)
- Infusion reaction cytokines/chemokines
  - Immediately prior to obinutuzumab dosing
  - 2 hours into obinutuzumab infusion
  - 4 hours into obinutuzumab infusion
- Adverse events

C1D2 and C1D8 Visits

- Adverse events
- Concomitant medications
- MRU (C1D8 Only)
- Study drug compliance review
- Physical exam (limited) (C1D8 Only)
- Vitals signs (C1D8 Only)
- ECOG performance status (C1D8 Only)
- Hematology (C1D8 Only)

C1D15 Visit

- Adverse events
- Concomitant medications
- MRU
- Study drug compliance review
- Physical exam (limited)
- Vitals signs
- ECOG performance status
- Hematology
- Biomarker assays
- PK Sampling (Subjects in Treatment Arm A only)
- Flow cytometry blood assays

8.2.1.2. Cycles 2 - 6 Visits

The following procedures will be performed on Day 1 (±3 days) of each cycle:

- PRO
- Adverse events
- Concomitant medications
- MRU
- Study drug compliance review
- Physical exam

- Vital signs
- ECOG
- CT/MRI scan (Cycle 5 Only)
- Overall response assessment (Cycle 5 Only)
- Hematology
- Serum chemistry (including creatinine clearance)
- Biomarker assays (Cycle 5 Only)
- Flow cytometry blood assays (Cycle 5 Only)
- PK Sampling (subjects in Treatment Arm A only – Cycle 2 Only)

The following procedures will be performed on Day 15:

- Study drug compliance review
- Hematology (may be performed locally)

8.2.1.3. Cycles 7 - 33 Visits

For subjects randomized to Treatment Arm A, **ibrutinib** therapy should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

The following procedures will be performed on Day 1 (±3 days) of Cycles 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 33:

- PRO
- Adverse events
- Concomitant medications
- MRU
- Study drug compliance review (ibrutinib only)
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry (including creatinine clearance) (Cycles 7, 9, 11, and 13, then every 4 cycles)
- CT/MRI Scan (Cycles 9, 13, 17, 21, 25, 29, and 33)

- Bone marrow biopsy/aspirate (Cycle 9 only, unless appropriate for evaluation of PD or CR or to confirm MRD negativity in the peripheral blood)
- Overall response assessment (Cycles 9, 13, 17, 21, 25, 29, and 33)
- Biomarker assays (Cycles 9, 13, 17, 21, 25, 29, and 33)
- Flow cytometry blood assays (Cycles 9, 13, 17, 21, 25, 29, and 33)
- Cytogenetics: FISH panel (Cycle 9 Only)

8.2.1.4. Cycle 36 - Disease Progression / Study Closure

For subjects randomized to Treatment Arm A, **ibrutinib** therapy should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

The following procedures will be performed every 3 cycles for Arm A starting on Day 1 (±3 days) of Cycle 36 and every 6 cycles for Arm B starting on Day 1 (±3 days) of Cycle 39 until disease progression or study closure:

- PRO
- Adverse events
- Concomitant medications
- MRU
- Study drug compliance review (ibrutinib only)
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry (including creatinine clearance)
- CT/MRI Scan (every 6 cycles beginning at Cycle 39)
- Bone marrow biopsy/aspirate (if appropriate)
- Overall response assessment (every 6 cycles beginning at Cycle 39)
- Biomarker assays (every 6 cycles beginning at Cycle 39)
- Flow cytometry blood assays (every 6 cycles beginning at Cycle 39)

8.2.1.5. Suspected Disease Progression Visit

The following procedures will be performed when Disease Progression is suspected:

- PRO

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- CT/MRI scan
- Bone marrow biopsy/aspirate (if appropriate)
- Overall response assessment
- Hematology
- Cytogenetics: FISH panel
- Biomarker assays
- Flow cytometry blood assays

8.2.2. End-of-Treatment Visit

The following will be performed 30 (±3) days after discontinuation of therapy (if the assessments do not coincide with regularly scheduled study assessments):

- PRO
- Adverse events
- Concomitant medications
- MRU
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry (including creatinine clearance)
- Biomarker assays
- Flow cytometry blood assays

8.3. Post-PD Follow-up Phase

Once subjects experience disease progression and are no longer eligible for ibrutinib monotherapy, they will be contacted approximately every 3 months (±14 days) by clinic visit or telephone to assess survival, the use of alternative anticancer therapy (and response to all subsequent anticancer therapies including best overall response for each regimen, whether the subject progressed following each regimen, and date of PD if applicable), and other malignancies. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

8.4. Treatment with Ibrutinib for Subjects on Arm B (Chlorambucil and Obinutuzumab)

Subjects randomized to Arm B who meet the criteria outlined in Section 8.4.1, can receive next-line therapy with ibrutinib and will follow the schedule in Appendix I. Treatment with ibrutinib can be continued until disease progression as determined by the investigator, or until they meet the criteria for withdrawal in Section 9. Subjects must meet all of the criteria for next-line therapy with ibrutinib listed in Section 8.4.1. With Medical Monitor approval, central labs are required to determine appropriateness for next-line ibrutinib.

8.4.1. Criteria for Next-line Ibrutinib Therapy

1. IRC confirmation of progression and Sponsor approval
2. ECOG Performance Status of ≤3 (Appendix B)
3. Platelet count ≥25,000/μL
4. No uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)
5. No currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix H), or history of myocardial infarction within 6 months prior to first dose with study drug
6. Recovered from the acute toxicities due to prior chemotherapy, radiotherapy, investigational drugs, or experimental treatments (non-hematologic toxicities have resolved to a NCI CTCAE [version 4.03] Grade of ≤2)
7. No known Richter's transformation
8. Does not require or receive anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)
9. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives,

some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) during the period of therapy and for 90 days after the last dose of ibrutinib, chlorambucil or obinutuzumab, and at least 18 months after the last obinutuzumab dose for female subjects. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion

10. No history of stroke or intracranial hemorrhage within 6 months

8.4.2. Next-line Ibrutinib Therapy Treatment Phase

Refer to the next-line ibrutinib therapy Schedule of Assessments (Appendix I) for a complete list of procedures to be performed at each scheduled study visit.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. 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.

9.2. Withdrawal from Study Treatment

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

- Progressive disease
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant
- Death

All subjects, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and be followed for progression and survival.

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

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.

9.3. Withdrawal from Study

Withdrawal 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)

10. STATISTICAL METHODS AND ANALYSIS

This section outlines statistical analysis approaches and methods for the study. Specific details for efficacy and safety analyses, including control of multiple testing procedures, will be described in the Statistical Analysis Plan (SAP).

10.1. General Considerations

10.1.1. Independent Review Committee (IRC)

The IRC will be chaired by a physician with expertise in CLL and SLL and will conduct response evaluations in accordance with the IRC charter.

10.1.2. Data Monitoring Committee (DMC)

The safety of this study will be monitored by an independent Data Monitoring Committee (DMC) as outlined in the DMC Charter and in accordance with the Sponsor's Pharmacovigilance procedures.

The independent DMC will be chaired by a physician with expertise in CLL and SLL. The DMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter. The Sponsor may attend only the blinded portion of the DMC meetings to answer questions as necessary. The DMC charter will provide provisions for restricted communications between the DMC and the Sponsor in the event the DMC recommends stopping the study for safety.

An early safety analysis will be performed after at least 6 subjects have been treated for approximately 4 weeks. This analysis will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs as well as events of special interest. This information will be reviewed by the Medical Monitor on an ongoing basis until this early safety analysis is conducted. The chair of the DMC, with involvement of the DMC statistician, as needed, will issue a recommendation as to whether the study should be interrupted during this period. If the DMC recommends the trial be continued, the DMC will review safety data periodically.

10.2. Randomization

Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, subjects will be randomized based on the following stratification factors:

- ECOG 0-1 vs 2
- Cytogenetics - will be stratified into one of three categories
  - del 17p
  - del 11q without del 17p
  - others (neither del 17p nor del 11q)

Subjects will be randomized in a 1:1 ratio to either Treatment Arm A or Treatment Arm B within each randomization stratum.

10.3. Sample Size Considerations

The sample size is calculated based on the assumptions:

- Randomization ratio of 1:1
- Median PFS of 27 months for Arm B (chlorambucil in combination with obinutuzumab)
- Target hazard ratio of 0.55, which corresponds to median PFS of 49.1 months for Arm A (ibrutinib combined with obinutuzumab).
- No interim analysis will be performed.

Assuming an enrollment rate of 18 subjects per month, approximately 212 eligible subjects will be enrolled to observe 94 PFS events in approximately 36 months from the first subject

randomized. On this basis, the study has at least an 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution for PFS.

This study is powered based on the primary endpoint PFS. The primary analysis of PFS will be performed when 94 confirmed progression/death events have occurred. The analysis of the secondary endpoint OS will be performed at the time of PFS primary analysis.

10.4. Interim Analysis

No interim analysis will be performed in this study.

10.5. Analysis Populations

10.5.1. Intent-to-Treat (ITT) Population

The ITT population is defined as all subjects who were randomized. Efficacy analysis will be performed using the ITT population; subjects will be analyzed as randomized. In addition, ITT population will be used to summarize demographics, and baseline and disease characteristics.

10.5.2. Safety Population

The safety population includes all subjects who received at least one dose of any one of the three study drugs (ibrutinib, chlorambucil, or obinutuzumab). The safety analysis will be performed using the safety population; and subjects in the safety population will be analyzed as treated.

10.5.3. Pharmacokinetic Evaluable Population

The PK-evaluable population includes subjects who received at least one dose of ibrutinib and had at least one post-treatment sample obtained.

10.5.4. Additional Analysis Populations

Additional analysis populations, which might be used for sensitivity analyses and biomarker studies, are defined in the SAP.

10.6. Control for Bias

The following study design components will facilitate the control for bias:

- Large (approximately 212 subjects)
- Multicenter
- Randomized

The randomization code will be controlled through a centralized procedure and will not be known to Sponsor personnel directly involved with study conduct or data analysis until after the final analysis. The key efficacy endpoints will be determined by the IRC who is independent to

any study procedure and treatment information. The detail information will be described in the study bias control plan.

10.7. Efficacy Analyses

10.7.1. Primary Endpoint and Methods

The primary efficacy endpoint is **Progression-free Survival** (PFS), which is defined as the time from the date of randomization until confirmed disease progression (assessed by the IRC per IWCLL 2008 criteria, with modification for treatment-related lymphocytosis) or death from any cause, whichever occurs first. Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. For subjects without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization. Adequate disease assessment is defined as physical examination and CBC, or CBC and CT scan. The detail of the statistical model and censoring rule will be described in SAP.

The analysis of PFS will be performed in the ITT population to compare PFS (as assessed by the IRC) for the two treatment arms using a log-rank test. Distribution of PFS including median and its corresponding 95% confidence interval (CI) will be summarized for each treatment arm using the Kaplan-Meier estimate. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model.

10.7.2. Secondary Endpoints and Methods

10.7.2.1. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of subjects who achieve a CR, CRi, nPR, or PR, over the course of the study as evaluated by the IRC using IWCLL 2008 criteria, with modification for treatment-related lymphocytosis. Subjects who do not have any post-baseline response assessment will be considered as nonresponders. A chi-square test will be used to compare the two treatment arms.

10.7.2.2. Rate of Minimal Residual Disease (MRD)-negative Responses

A chi-square test will be used to compare the rate of MRD-negative responses between the two treatment arms.

10.7.2.3. Overall Survival

Overall survival is defined as the time from date of randomization until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. The analysis of the secondary endpoint OS will be performed at the time of PFS primary analysis. Similar to PFS, OS will be analyzed using log-rank test and Cox proportional hazards model.

- The null hypothesis is HR (hazard ratio for Arm A vs Arm B) ≥1 and the alternative hypothesis is HR<1.
- With an alternative HR of 0.39, 33 deaths at the analysis for primary endpoint provides approximately 69% power, based on a log-rank test, a 1-sided overall significance level of 0.025 and 229 randomized subjects.

EAST 6.4 was used for the power calculation and the calculation of the alternative HR of 0.39 is based on the estimated 36-months OS rate of 76% for Arm B (based on the 36-month landmark survival rate of obinutuzumab + chlorambucil arm from Figure 1 of Gazyva® Prescribing Information and the estimated 36-months OS rate of 90% for Arm A (estimated from 30-month landmark OS rate in ibrutinib arm from the Sponsor's Study PCYC-1115-CA).

As an example, Table 7 provides estimates of the events and power.

Table 7: The Predicted HR and Total Expected Events for OS

36-month OS Rate Ibrutinib + Obinutuzumab	36-month OS Rate Chlorambucil + Obinutuzumab	HR	Power	Total Number of Events
0.899	0.74	0.355	78%	35
0.88	0.74	0.425	68%	37
0.899	0.76	0.39	69%	33
0.88	0.76	0.466	57%	35
0.899	0.78	0.431	59%	31
0.88	0.78	0.515	45%	33

10.7.2.4. Hematological Improvement

Hematological improvement will be evaluated in all subjects and in the subset of subjects with cytopenia(s) at baseline (Hgb ≤11 g/dL, or platelets ≤100,000/μL), improvement is defined as an increase of Hgb levels from baseline by ≥2 g/dL, or an increase of platelet counts from baseline by ≥50%. Improvement will be assessed in all subjects at Cycle 9 Day 1 response assessment. Sustained hematologic improvement is defined as hematological improvement that sustained continuously for ≥56 days without blood transfusion or growth factors.

Percentage of subjects with sustained improvement will be compared using χ^2 test.

10.7.2.5. Patient Reported Outcome (PRO) by EQ-5D-5L

For EQ-5D-5L, the scores for the five categorical dimensions will be used to compute a single utility score ranging from zero (0.0) to one (1.0) representing the general health status of the subject. The United Kingdom weights will be used to generate subject utilities from the five dimensions.

The change in utility score from baseline will be summarized. Methods will be detailed in SAP.

10.7.3. Exploratory Endpoints and Methods

The exploratory endpoints will be evaluated to comparing the treatment effects between two treatment arms. Descriptive statistics will be used to summarize these exploratory endpoints. The details will be provided in the SAP.

10.7.3.1. Event-free Survival

Event-free survival is measured by the absence of events defined by progressive disease (PD), death, and nonresponders.

10.7.3.2. Time to Next Treatment (TTNT)

Time to next treatment (TTNT) is defined as the time from randomization to institution of any subsequent treatment for CLL/SLL (including the next line ibrutinib for subjects in arm B).

10.7.3.3. Clonal Evolution

The proportion of subjects with new cytogenetic abnormalities (del 11q, del 17p, or trisomy 21), or other cytogenetic abnormalities detected by FISH, cytogenetics, or mutational analysis at any time post commencement of study treatment will be determined.

10.7.3.4. Predictive Biomarkers of Efficacy and/or Mechanism of Resistance

Biomarker exploratory analyses are planned to identify biomarkers that may associate with response (or resistance) to ibrutinib. These biomarkers include but are not limited to secreted protein analysis, genomic and expression analysis.

10.7.3.5. Medical Resource Utilisation

Parameters collected for MRU associated with the therapy include number of hospitalizations, number of emergency department visits, number of blood product transfusions, and number of use of hematopoietic growth factors.

10.7.3.6. Sparse Pharmacokinetic Characteristics of Ibrutinib

The plasma concentration data for ibrutinib will be summarized using descriptive statistics at each timepoint. Population PK analysis of plasma concentration-time data of ibrutinib will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant population PK model. Available subject characteristics (eg, demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

10.7.3.7. Genetic and Molecular Prognostic Markers

Genetic and molecular prognostic markers will be summarized with descriptive statistics.

10.8. Safety Analyses

Safety summaries will include tabulations in the form of tables and listings. The safety analysis will be conducted using the safety population. Subjects will be analyzed according to the actual treatment received.

Study drug exposure including duration and dosage as well as dose modifications of study drug including dose reduction, dose delay, missed doses, and dose interruption will be summarized.

10.8.1. Adverse Events (AEs)

Adverse events (AEs) will be graded by the Investigator according the NCI CTCAE v4.03 for non-hematological AEs. Hematologic toxicity will be assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies. Verbatim descriptions of AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events that started from the date of the first dose of the first study drug up to 30 days after the date of the last dose of the last study drug, or the first date starting new anticancer therapy, whichever is earliest, are considered treatment-emergent except treatment related AEs. Any treatment related AE will be considered treatment-emergent regardless of the start date of the event. Any event that is present at baseline but worsens in severity or is subsequently considered treatment-related by the investigator will also be considered as treatment-emergent. All-treatment emergent AEs will be summarized by treatment arm. The incidence rates of treatment-emergent AEs will be summarized by System Organ Class (SOC), preferred term, toxicity grade, and relationship to study drug. In addition, SAEs, Grade 3 or above AEs, AEs leading to study treatment discontinuation, delay, reduction, or interruption, AEs leading to death, and events of special interest will be summarized. Multiple occurrence of the same event in a given subject will be counted once at the maximum severity and strongest relationship to study drug.

AEs leading to death and non-fatal SAEs will be listed by subject and tabulated by preferred term.

10.8.2. Laboratory Evaluations

All laboratory values will be converted to standard international (SI) units and classified as normal, low, or high based on normal ranges supplied by the central laboratory. Hematologic parameters including platelet count, hemoglobin, and neutrophils will be assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03.

Subjects with values outside the normal range will be flagged and summarized by treatment arm. Selected gradable laboratory parameters will be summarized by treatment arm using shift tables. A separate listing and table will be provided to identify and summarize subjects with markedly abnormal changes. In addition, changes from baseline in quantitative parameters will be summarized descriptively by treatment arm at scheduled timepoints.

10.8.3. Vital Signs

Vital signs will be classified as normal, low, or high; and change from baseline will be summarized descriptively by treatment arm at scheduled timepoints. Subjects with markedly abnormal changes will be listed and tabulated.

10.8.4. Obinutuzumab-related Infusion Reactions

The proportion of subjects experiencing i) no infusion reactions, ii) Grade 1 and/or Grade 2 infusion reactions or iii) Grade 3 and/or Grade 4 infusion reactions will be evaluated for each treatment arm for i) Cycle 1 of obinutuzumab and ii) all other cycles of obinutuzumab (Cycles 2 and subsequent cycles).

The secreted protein analysis will also be used to evaluate the impact of ibrutinib on obinutuzumab-related infusion reactions. Plasma will be collected pre-dose ibrutinib/chlorambucil, immediately prior to infusion of obinutuzumab, and 2 and 4 hours into the obinutuzumab infusion on Day 1. The samples will be evaluated for secreted proteins related to infusion reactions, such as IL-6, TNF-alpha, as well as other cytokines and chemokines.

10.8.5. Other Safety Assessments

Physical examination, ECG, and eye examination results will be listed.

11. 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.

11.1. Definitions

11.1.1. 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 adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease 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 AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) 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 informed consent form 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. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.1.2. Serious Adverse Events

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

- Results in death (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 which 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 inpatient 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.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of nonhematologic AEs. Refer to Appendix D for the grading of hematologic 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 which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which 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 which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. 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.

11.2. 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.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any 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/subject exposure to the study drug, eg, name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events eCRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

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. SAEs will be reported to the Sponsor from the time of ICF signing. Both serious and non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (see Section 11.1.1).

All adverse events, 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 (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

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. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

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

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/ discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

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

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

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of ibrutinib or chlorambucil, and at least 18 months after the last dose of obinutuzumab. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of ibrutinib, chlorambucil or obinutuzumab. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. 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. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

11.4.6. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.6.1. 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 11.4.6 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. 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.

12.2. 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 Pharmacyclics 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.

12.3. 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.

12.4. 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 the 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).

12.5. 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 7.1.1.1), 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 Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics 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.

12.6. 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 Pharmacyclics 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 Pharmacyclics and obtain written approval from Pharmacyclics 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.

Pharmacyclics must be notified in advance of, and Pharmacyclics 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 Pharmacyclics 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.

12.7. 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 a reasonable period of time. 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 Pharmacyclics 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.

12.8. 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 Pharmacyclics.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics 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-1130-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 Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics 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.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics 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 Pharmacyclics, 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.

Pharmacyclics 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, Pharmacyclics 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.

12.10. 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.

12.11. 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.

12.12. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics 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 personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. 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.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, 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.

12.14. Protocol Amendments

Pharmacyclics 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 Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial. Any substantial change to the protocol, including any change in risk, must also be approved by the applicable national and/or local regulatory authorities prior to implementation at each site.

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 Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics 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, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics 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 Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. 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.

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14. APPENDICES

Appendix A. Schedule of Assessments

Study Visits		Screening Phase	Pre-PD Phase - (1 cycle = 28 days)[z]								Suspected PD	End-of-Treatment	Post-PD FU
			Cycle 1				Cycles 2–6 Every Cycle		Cycles 7–33 Every Odd Cycle	Arm A: Cycles 36 - PD (q3 Cycles) Arm B: Cycles 39 - PD (q6 Cycles)[y]	As soon as possible after suspected PD	Within 30 Days after treatment d/c[b]	q3 months
			D1 (baseline)[a]	D2	D8	D15	D1	D15	D1	D1			
Study Visit Windows		-30 days					± 3 days				Any time	± 3 days	± 14 days
Study Drug Administration and Dispensation													
ARM A	ibrutinib 420 mg PO + Obinutuzumab 1000 mg IV		**ibrutinib:** 420 mg PO daily[c] **Obinutuzumab:** 1000 mg IV Cycle 1: D1(100 mg), D2 (900 mg), D8 (1000 mg), D15 (1000 mg) Cycle 2 – Cycle 6: D1 (1000 mg)						**ibrutinib:** 420 mg PO daily[c]				
ARM B[d]	Chlorambucil 0.5 mg/kg PO[e] + Obinutuzumab 1000 mg IV		**Chlorambucil:** 0.5mg/kg PO[e,f] Cycle 1 – Cycle 6: D1 & D15 **Obinutuzumab:** 1000 mg IV Cycle 1: D1(100 mg), D2 (900 mg), D8 (1000 mg), D15 (1000mg) Cycle 2 – Cycle 6: D1 (1000 mg)										
Procedures													
Informed consent		X											
Medical history		X											
Confirm eligibility and randomize[g]			X										
Patient-reported outcomes (PRO)[h]		X	X				X		(X)	(X)	X	X	
Cumulative Illness Rating Scale (CIRS)		X											
Concomitant medications		X	X	X	X	X	X		(X)	(X)	X	X	
Adverse events[i]		X	X	X	X	X	X		(X)	(X)	X	X	
Medical resources usage (MRU)					X	X	X		(X)	(X)		X	
Study drug compliance review[j]			X	X	X	X	X	X	(X)	(X)	X	X	
Physical exam, vital signs, height, weight, ECOG[k]		X	X		X[l]	X[l]	X		(X)	(X)	X	X	

Study Visits	Screening Phase	Pre-PD Phase - (1 cycle = 28 days) [z]								Suspected PD	End-of-Treatment	Post-PD FU
		Cycle 1				Cycles 2–6 Every Cycle		Cycles 7–33 Every Odd Cycle	Arm A: Cycles 36 - PD (q3 Cycles) Arm B: Cycles 39 - PD (q6 Cycles) [y]	As soon as possible after suspected PD	Within 30 Days after treatment d/c[b]	q3 months
		D1 (baseline)[a]	D2	D8	D15	D1	D15	D1	D1			
Study Visit Windows	-30 days	± 3 days								Any time	± 3 days	± 14 days
CT/MRI scan	X[m]					(X)[n o]		(X)[o]	(X)[o]	X		
Bone marrow biopsy/aspirate	X[p]							(X)[p]	(X)[p]	(X)		
Overall response assessment[q]						(X)[n]		(X)[o]	(X)[o]	X		
Pregnancy	X	X										
Hematology	X	X		X	X	X	X[r]	(X)	(X)	X	X	
Serum chemistry	X	X				X		(X)[x]	(X)[x]		X	
Creatinine clearance (Cockcroft-Gault)	X	X				X		(X)[x]	(X)[x]		X	
Cytogenetics: FISH panel / TP53 assay	X							(X)[s]		X		
Hepatitis serologies	X											
Coagulation panel	X											
Biomarkers Assays		X			X	(X)[n]		(X)[o]	(X)[o]	X	X	
Flow cytometry blood assays		X			X	(X)[n]		(X)[o]	(X)[o]	X	X	
Infusion reaction cytokines/chemokines [t]		X										
Genetic/molecular prognostic factors	X											
12-lead ECG [u]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)										
Survival, including other malignancies												X
Any new anticancer therapy												X
Substudies												
PK sample collection for ARM A only					(X)[v]	(X)[w]						

D = day; Term = treatment termination; d/c = discontinuation; PD = progressive disease; FU = follow-up; (x) = not all visits or all subjects

Footnote:

a. C1D1: To be collected pre-dose, unless otherwise specified

b. End-of-Treatment Visit: may be sooner if subject is scheduled to start a new anticancer treatment. Also, the End-of-Treatment Visit will be performed 30 (± 3) days after discontinuation of therapy (if the assessments do not coincide with regularly scheduled study assessments).

c. Ibrutinib: Day 1 dose of Cycle 1 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

d. For Arm B subjects: if PD is confirmed and the IWCLL treatment guidelines indicate that new anticancer therapy is indicated, second-line treatment plan is established and subsequent assessments are as described in Appendix I.
e. Chlorambucil: dose based on most recent Day 1-documented weight.
f. Chlorambucil: Day 1 dose of every cycle (Cycles 1 to 6) and Day 15 dose of Cycle 1 should be taken at the investigational site. Starting on Cycle 2, Day 15 of each cycle may be self-administered at home.
g. Confirmation of eligibility and randomization may occur within 3 days.
h. PRO: EQ-5D-5L should be completed prior to any other procedures or physician interactions (after informed consent).
i. Adverse Events: AEs are reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events.
j. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration
k. Physical Exam: Height will only be taken at the Screening Phase. Vital signs through end of treatment only. ECOG through progressive disease. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.
l. Physical Exam: Cycle 1 D8 and D15 will have limited physicals.
m. CT Scan: Baseline CT scan can be performed up to 6 weeks prior to randomization.
n. Biomarkers/Flow Cytometry: Cycle 5 only.
o. CT Scan/Overall Response/Biomarkers/Flow Cytometry: Every 4 cycles after Cycle 5 (Cycles 9, 13, 17, 21, 25, 29, 33), then these will occur every 6 cycles thereafter. If study drug is held before a scheduled response assessment then the response assessment can be delayed up to 4 weeks to allow re-initiation of study drug for 2 weeks (or as long as possible) prior to performing scheduled response assessment.
p. Bone marrow biopsy and aspirate: should be performed at Screening or up to 90 days before the first dose of study drug, at Cycle 9 (A bone marrow aspirate will not be required at Cycle 9 for subjects who have unequivocal evidence of ongoing gross clinically detectable disease (eg, lymph node >2cm), however these subjects should have a peripheral blood sample sent for MRD analysis and a bone marrow aspirate should be considered for the next scheduled response assessment visit), and as needed to confirm complete response (CR) or evaluate cytopenia. Bone marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; all responders who have an MRD-negative status in the bone marrow, should be followed with peripheral blood MRD analyses every 4 cycles until Cycle 33 then every 6 cycles starting at Cycle 39. All responders who have an MRD-positive status in the bone marrow or peripheral blood, should also be followed with peripheral blood MRD assessments every 4 cycles until Cycle 33 then every 6 cycles starting at Cycle 39. Once the subject becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment. Additionally, a peripheral blood sample will be taken at Cycle 9.
q. Overall Response: If study drug is held before a scheduled response assessment then the response assessment can be delayed up to 4 weeks to allow re-initiation of study drug for 2 weeks (or as long as possible) prior to performing scheduled response assessment.
r. Hematology: Cycles 2-6 Day 15 hematology can be performed locally.
s. Cytogenetic, FISH panel, and TP53: Assay should be performed at Cycle 9.
t. Infusion Reaction: Plasma sample will be collected at pre-dose ibrutinib/chlorambucil, immediately prior to infusion of obinutuzumab, and 2 and 4 hours into the obinutuzumab infusion.
u. ECG: At Screening, 12-lead ECGs will be done *in triplicate* (≥1 minute apart). ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.
v. PK (Arm A only): Cycle 1, Day 15: Pre-dose (window: 30-60 minutes before dose), then 1 hour (window: 45-75 minutes), 2 hours (window: 1.5-2.5 hours), and 4 hours (window: 3.5-4.5 hours) post-dose.

w. PK (Arm A only): Cycle 2, Day 1: To be collected pre-dose only (window: 30-60 minutes before dose).
x. Serum chemistry, including creatinine clearance, will only be taken at Cycles 7, 9, 11, 13, 17, 21, 25, 29, 33, and every 6 cycles until PD.
y. Protocol visits for subjects on Arm B will occur every 6 cycles until PD beginning at Cycle 39.
z. All subjects randomized to study treatment will continue following all study procedures and visits following the pre-PD schedule until disease progression, including subjects on Arm B who complete treatment and any subjects who discontinue study treatment early.

Appendix B. ECOG Status Scores

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

**Oken, MM, et al.1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008.

Appendix C. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

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
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
Posaconazole[a]	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole[a]	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

a. Classification based on internal data.

Appendix D. Hematologic Adverse Event Grading Scheme (Hallek 2008)

An evaluation of the hematologic toxicity in patients with advanced CLL/SLL must consider the high frequency of marrow involvement and previous exposure to chemotherapy with consequent medullary compromise at the initiation of therapy. The standard hematologic grading system for solid tumors cannot, therefore, be directly applied. A substantial proportion of patients would be considered to have Grade 2 to 4 hematologic toxicity before any therapy is given. Note that only hematological toxicities deemed Clinically Significant should be recorded as Adverse Events. Therefore, the following modified schema will be used to quantitate hematologic deterioration in patients with CLL/SLL.

Hematologic Grading Scheme

Decrease in Platelets or Hgb (Nadir) from Pre-treatment Value, %	ANC/μL (nadir)[c]	Toxicity Grade
0 - 10%[a]	≥ 2000	0
11 - 24%[a,b]	≥ 1500 and < 2000	1
25 - 49%[a,b]	≥ 1000 and < 1500	2
50 - 74%[a,b]	≥ 500 and < 1000	3
> 75%[a,b]	< 500	4

a. If at any level of decrease, the platelet count falls below 20×10^9/L, toxicity will be considered Grade 4. If the baseline platelet count is $<20 \times 10^9$/L, platelet toxicity cannot be evaluated.

b. Baseline and subsequent Hgb values must be determined the day of any given transfusion.

c. If the ANC was <1000/μL before therapy, the patient is not evaluable for toxicity referable to the ANC.

Appendix E. EQ-5D-5L

(English version for the UK)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

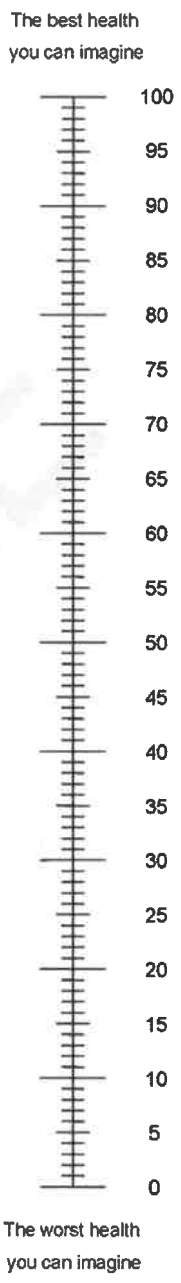
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

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

YOUR HEALTH TODAY = ☐



Appendix F. Cumulative Illness Rating Scale (CIRS)

Please take into account that CLL induced illness or organ damage are not included in this rating scale. The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are two or more illness/impairments of one organ system, the illness/impairment with the highest severity should be evaluated.

Organ system	If illness/impairment present, specify the illness/impairment with highest severity	Score
Cardiac	_____	_____
Hypertension	_____	_____
Vascular	_____	_____
Respiratory	_____	_____
Eye/ear/nose/throat/larynx	_____	_____
Upper gastrointestinal	_____	_____
Lower gastrointestinal	_____	_____
Hepatic/biliary	_____	_____
Renal	_____	_____
Genitourinary	_____	_____
Musculoskeletal	_____	_____
Endocrine/metabolic	_____	_____
Neurological	_____	_____
Psychiatric	_____	_____
	Total score	_____

CIRS Rating of Comorbidity

Score		
0	No problem	Organ system not compromised.
1	Mild	Illness/impairment with or without requirement of therapy, excellent prognosis, patient with normal activity
2	Moderate	Illness/impairment requiring therapy, good prognosis; compromised activity of patients
3	Severe	Illness/impairment with urgent requirement for therapy, prognosis unclear, marked restriction in activity of patient.
4	Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis.

Appendix G. Rai Staging

Rai Stage
0 Lymphocytes (L) in blood (>5000/μL)
I L + enlarged lymph nodes (LN)
II L + spleen and/or liver (LN positive or negative)
III L + anemia (Hgb <11g/dL)
IV L + thrombocytopenia (platelets <100,000/μL)

Appendix H. New York Heart Association Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Appendix I. Schedule of Assessments for Subjects Treated with Chlorambucil and Obinutuzumab (Arm B) who are to Receive Next-line Ibrutinib Therapy

Study Weeks	Assessment for Next-line Ibrutinib Therapy	Treatment Phase[d]			Follow-up Phase
		Every 4 weeks for 24 weeks	Every 12 weeks until PD	End-of-Treatment Visit	Follow-up (Every 12 weeks)
Study Windows	±14 d	±7 d	±7 d	30 (±3 d)	±7 d
Study Drug Administration					
Ibrutinib 420 mg per day PO		Continuous Daily Dosing			
Procedures					
Medical Monitor approval	x				
Concomitant medications	x	x	x	x	
Adverse events		x	x	x	
Physical examination (including Lympathic Exam), vital signs, ECOG	x	x	x	x	
Hematology	x	x[a]	x	x	
Serum chemistry	x				
Investigator assessment of response and for progression[b]		x	x		
Survival status					x[c]
Subsequent anticancer therapies					x[c]
Predictive Biomarkers	x				

CLL=chronic lymphocytic leukemia; d=day(s); ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; PD=progressive disease; PO=oral; qd=once daily

a. CBC should be performed weekly for the first 4 weeks

b. Efficacy assessments should include CT scan every 24 weeks until the first disease progression on protocol. For subjects who have had experienced PD and are crossed over to ibrutinib, CT scans for response assessments may be performed at investigator's discretion.

c. Survival and subsequent anticancer therapy status will be collected by telephone

d. Subjects will follow the following visit schedule of the Treatment Phase, performing the applicable procedures outlined in the Table on Day 1 of each cycle – Cycle 1 (C1D1, C1D8, C1D15, C1D22 – includes weeks 1, 2, 3, 4 for CBC only), C2 (week 5), C3 (week 9), C4 (week 13), C5 (week 17), C6 (week 21), C7 (week 25), C10 (week 37), C13 (week 49), then continue every 3 cycles (12 weeks) until disease progression or study closure.

Appendix J. Child-Pugh Score for Subjects with Liver Impairment

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

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

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.