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PROTOCOL

TITLE:	Phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naïve chronic lymphocytic leukemia / small lymphocytic lymphoma
PROTOCOL NUMBER:	**PCYC-1142-CA**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EudraCT NUMBER:	2016-002293-12
SPONSOR MEDICAL MONITOR:	[redacted] Pharmacyclics LLC Phone: [redacted] Fax: Email:
SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
DATE FINAL:	05 July 2016
Amendment 1:	25 September 2017
Amendment 2:	29 November 2018
Amendment 3:	11 September 2019

Confidentiality Statement

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1142-CA entitled "Phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment naïve chronic lymphocytic leukemia / 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

[redacted] authorized to sign the protocol and any

14 Sep 2019

Medical Monitor's Signature Date

[redacted]

Clinical Science, Pharmacyclics LLC

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SYNOPSIS

Study Title:	Phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment naïve chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL)
Protocol Number:	PCYC-1142-CA
Study Phase:	2
Study Duration:	Estimated to be 7 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Venetoclax will be supplied as 10 mg, 50 mg, and 100 mg film coated tablets for oral (PO) administration.
Objectives:	**MRD Cohort** ***Primary Objective:*** To evaluate if discontinuing ibrutinib, in the setting of a confirmed MRD-negative response with the combination of ibrutinib + venetoclax, allows for a treatment holiday as assessed by 1-year disease-free survival (DFS). ***Secondary Objectives***: To evaluate: • Minimal Residual Disease (MRD) – negative rate • Overall response rate (ORR) • Complete response rate (Complete Response [CR], and CR with incomplete marrow recovery [CRi]) • Duration of response (DOR) • Tumor Lysis Syndrome (TLS) risk reduction • Progression free survival (PFS) • Overall survival (OS) • Pharmacokinetics of ibrutinib and venetoclax when dosed in combination • Safety and tolerability

	Fixed Duration Cohort ***Primary Objective:*** To evaluate the depth of response with the combination of ibrutinib + venetoclax administered for a fixed duration of therapy by assessment of complete response (CR/CRi) rate. ***Secondary Objectives:*** To evaluate: • Duration of Response (DOR) • Minimal Residual Disease (MRD)-negative rate • Overall response rate (ORR) • Tumor Lysis Syndrome (TLS) risk reduction • Progression free survival (PFS) • Overall survival (OS) • Safety and tolerability
Study Design:	This is a multicenter, 2-cohort Phase 2 study assessing both MRD-guided discontinuation and fixed duration therapy with the combination of ibrutinib + venetoclax in subjects with treatment-naïve CLL or SLL. The study consists of an MRD cohort and a Fixed Duration cohort. All subjects who discontinue treatment in the absence of disease progression will remain on study until confirmed disease progression or until study closure. All subjects who discontinue for disease progression will be followed for survival and subsequent anti-cancer therapies. Details of the sequentially designed and enrolled MRD and Fixed Duration cohorts are below. 1. **MRD Cohort:**

	The MRD cohort portion of the study consists of a pre-randomization phase (combination treatment phase), an MRD-guided randomization phase, and a post-PD follow-up phase. Please see Section 3.1 for full explanation of study design. Investigator assessment of disease overall response and progression will be based upon IWCLL criteria (Hallek 2008, Hallek 2012, Hallek 2013). Imaging will be collected and stored centrally. The primary analysis will be performed at the point that all randomized subjects have had the opportunity to complete approximately 12 cycles of randomized treatment or follow-up. All safety and efficacy endpoints will be analyzed at the time of the primary analysis. After the primary analysis, the Sponsor may elect to discontinue follow-up of specific MRD cohort treatment arms on PCYC-1142-CA. Subjects who are on ibrutinib at the time of study arm closure may be offered a separate extension study to continue ibrutinib. **Pre-randomization Phase** Approximately 150 subjects will be enrolled into this phase. The subjects will receive single-agent ibrutinib for 3 cycles followed by ibrutinib + venetoclax combination treatment for at least 12 cycles. The safety of ibrutinib + venetoclax combination therapy will be assessed by a Data Review Committee (DRC). Approximately 12 subjects will be enrolled in a Safety Run-in Period to assess tolerability in the first 6 evaluable subjects who complete venetoclax dose escalation (3 cycles of ibrutinib treatment followed by the addition of venetoclax administered by standard 5-week dose ramp-up, plus an additional week of follow up). Enrollment will be held until the safety and tolerability of the combination therapy is confirmed by the DRC. Subjects will be assessed for MRD status in peripheral blood (PB) every 3 cycles starting after completion of 6 cycles (C7D1), and in bone marrow (BM) aspirate after completion of Cycle 15 (C16D1). MRD assessment will be performed using flow cytometry with a sensitivity of $\geq 10^{-4}$. An early assessment of the MRD-negative response rate for the combination therapy will be assessed among the first 30 subjects who complete 9 cycles of combination treatment. The sample size may be adjusted accordingly based on this early assessment to adequately power for the Randomization Phase primary endpoint. MRD-negative response for randomization purposes must be confirmed serially over at least 3 cycles and is required to demonstrate negativity in both the bone marrow and peripheral blood. **Randomization Phase** Eligible subjects will be randomized in a 1:1 ratio based on their MRD status (see below). Subjects will be stratified by immunoglobulin heavy-chain variable region (IGHV) status in each randomization strata. <u>Randomization Phase - MRD-negative subjects (Double-blind):</u>

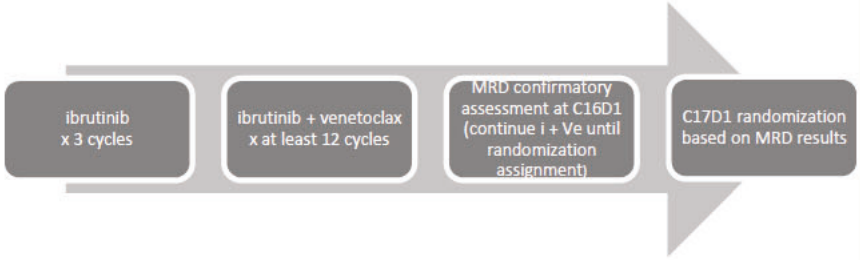
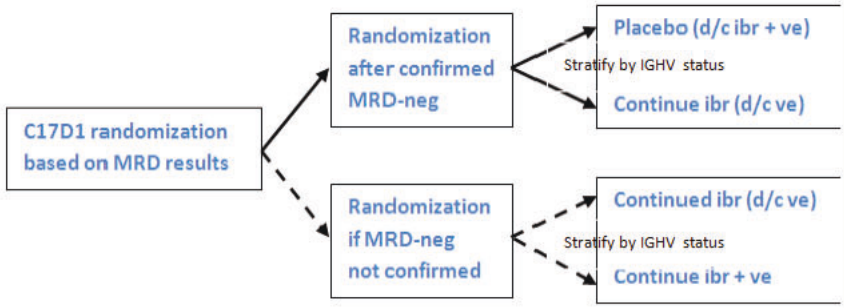
	Eligible subjects who achieve a confirmed MRD-negative response and who continue on ibrutinib will be randomized to receive blinded treatment of ibrutinib (venetoclax discontinued) vs placebo (ibrutinib and venetoclax discontinued). The randomization will be stratified by IGHV status. Subjects will be assessed for disease-free survival as measured by continued MRD-negative response without progression or death at least 1 year after randomization. MRD status will be evaluated every 3 cycles in PB. MRD should also be reassessed in BM aspirate after an additional 12 cycles. Randomization Phase - MRD-positive subjects (Open-label): Those subjects who do not achieve a confirmed MRD-negative response after 12 cycles of the combination and continue on treatment will be randomized to receive open label treatment of ibrutinib + venetoclax vs ibrutinib alone (venetoclax discontinued). The randomization will be stratified by IGHV status. Subjects will be assessed for MRD-negative response. MRD status will be evaluated every 3 cycles in PB. MRD should also be reassessed in BM aspirate after an additional 12 cycles and at any time in subjects who become MRD-negative in PB. For subjects receiving ibrutinib + venetoclax, venetoclax can be administered for up to approximately 2 years per treatment course, until PD or unacceptable toxicity, or until this arm's study closure, whichever is earlier. Subjects who are continuing on ibrutinib at the time of study arm closure may be offered a separate extension study to continue ibrutinib. Reintroduction of therapy**:** MRD-negative randomized subjects who experience confirmed MRD-positive relapse and/or confirmed disease progression may have their randomization unblinded, and may receive reintroduced therapy as follows: *Placebo subjects*: Subjects on the placebo arm will be offered the opportunity to reintroduce ibrutinib to assess if they can benefit from single-agent ibrutinib under the following circumstances: • For confirmed MRD-positive relapse and/or for disease progression by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, subjects will receive ibrutinib until PD or unacceptable toxicity. Ibrutinib reintroduced subjects who subsequently have confirmed disease progression by IWCLL criteria may continue ibrutinib and add venetoclax per standard dose ramp up *Ibrutinib subjects*: Subjects on the ibrutinib arm will be offered the opportunity to continue ibrutinib and reintroduce venetoclax treatment under the following circumstances: • For confirmed MRD-positive relapse and/or for confirmed disease progression by IWCLL criteria, subjects can continue ibrutinib and add venetoclax, per standard dose ramp up

	MRD-positive randomized subjects can receive reintroduced therapy as follows: *Ibrutinib only subjects*: Subjects on the ibrutinib arm will be offered the opportunity to continue ibrutinib and reintroduce venetoclax treatment per standard dose ramp up under the following circumstances: • For confirmed disease progression by IWCLL criteria, subjects will receive ibrutinib and venetoclax For MRD-negative and MRD-positive subjects who have reintroduced venetoclax, venetoclax can be administered for up to 2 years per treatment course, until PD or unacceptable toxicity, or until these arms' study closure, whichever is earlier. Subjects who are continuing on ibrutinib at time of study arm closure may be offered a separate extension study to continue ibrutinib. **Post-PD Follow-up Phase:** Subjects who have confirmed disease progression by IWCLL criteria and have discontinued study treatment will be followed for survival status and subsequent anti-cancer therapy until study closure. 2. **Fixed Duration Cohort** Approximately 125 subjects without del17p will be enrolled into this cohort sequentially after the MRD cohort. Subjects will receive 15 cycles of open label therapy consisting of single-agent ibrutinib for 3 cycles followed by ibrutinib + venetoclax combination treatment for 12 cycles. Investigator assessment of tumor response and progression will be based upon IWCLL criteria (Hallek 2008, Hallek 2012, Hallek 2013). Imaging will be collected and stored centrally. Subjects will be assessed for MRD status in peripheral blood (PB) every 3 cycles starting after completion of 6 cycles (C7D1), and in bone marrow (BM) aspirate after completion of 9 cycles (C10D1) and 3 months after completion of the fixed duration of therapy (ie, C19) or earlier if BM is obtained per clinical indication. MRD assessments will be performed using flow cytometry with a sensitivity of $\geq 10^{-4}$. The primary analysis will be performed when a clinically meaningful evaluation of durable CR rate (12 months or longer) can be assessed in the study population. FD Cohort subjects will be followed for approximately 5 years. Subjects who are continuing on ibrutinib at FD cohort study closure may be offered a separate extension study to continue ibrutinib. Reintroduction of therapy**:** Subjects with confirmed progression by IWCLL criteria after completion of the fixed duration regimen can be retreated with continuous single agent ibrutinib, or retreatment with the ibrutinib + venetoclax fixed duration treatment regimen may be considered based on Investigator's clinical discretion and Medical Monitor approval.

	Post-PD Follow-up Phase: Subjects will be followed for progression, overall survival (OS), and use of subsequent anticancer agents until study closure.
Population:	Subjects who have treatment-naive CLL or SLL with active disease requiring therapy
Centers:	Multiple, US vs. ex-US
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. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment: • Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia • Massive, progressive, or symptomatic splenomegaly • Massive nodes or progressive or symptomatic lymphadenopathy • Progressive lymphocytosis • Constitutional symptoms 3. Measurable nodal disease by computed tomography (CT). *Laboratory* 4. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days, (with the exception of pegylated G-CSF [pegfilgrastim] and darbopoeitin which require at least 14 days) prior to screening laboratory assessment defined as: • Absolute neutrophil count (ANC) >750/µL (750 cells/mm^3 or 0.75 x 10^9/L) • Platelet count >30,000 /µL (30,000 cells/mm^3 or 30 x 10^9/L). • Hemoglobin >8.0 g/dL 5. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN) • Creatinine Clearance (CrCl) ≥60 mL/min (eg, as estimated by Cockcroft-Gault) • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) 6. Prothrombin time (PT)/International normal ratio (INR) <1.5 x ULN and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). *Demographic* 7. Men and women ≥18 and ≤70 year of age.

	8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. *Ethical/Other* 9. 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. 10. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug. Male subjects must agree to refrain from sperm donation until 90 days after the last dose of study drug.
Exclusion Criteria:	1. Any prior therapy (including but not limited to chemotherapy, targeted therapy, immunomodulating therapy, radiotherapy, and/or monoclonal antibody) used for treatment of CLL or SLL. 2. History of other malignancies, except: • 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 the treating physician • Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease • Adequately treated carcinoma in situ without current evidence of disease 3. Known or suspected history of Richter's transformation. 4. Concurrent administration of >20 mg/day of prednisone within 7 days of initiation of study drug unless indicated for prophylaxis, or management of allergic reactions (eg, contrast). 5. Known hypersensitivity to one or more study drugs. 6. Known allergy to xanthine oxidase inhibitors and/or rasburicase. Subjects who are allergic to xanthine oxidase inhibitors and cannot receive rasburicase will be excluded. 7. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 8. Recent infection requiring systemic treatment that is ongoing or was completed ≤14 days before the first dose of study drug, or any uncontrolled active systemic infection. 9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).

	10. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 11. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBs Ag), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 12. Major surgery within 4 weeks of first dose of study drug. 13. 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. 14. 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 enrollment. 15. Unable to swallow capsules/tablets 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. 16. Concomitant use of warfarin or other vitamin K antagonists. 17. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix G). 18. Currently active, clinically significant hepatic impairment Child-Pugh Class B or C according to the Child Pugh classification (see Appendix K). 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). 22. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia 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 treat or control the autoimmune disease.

Study Treatment:	**1) MRD Cohort** **Pre-randomization Phase: ibrutinib + venetoclax combination**  *Ibrutinib*: • Orally once daily ibrutinib 420 mg (3 capsules) • Single-agent lead-in for 3-cycles, then continued in combination for at least 12 additional cycles until completion of Cycle 16 • Dose modification for adverse events are specified in Section 5.4.1.4 *Venetoclax*: • Orally once daily venetoclax, with 5-week dose ramp up (VENCLEXTA® [venetoclax] prescribing information), added to ongoing ibrutinib therapy starting at Cycle 4 and continuously for at least 12 cycles until completion of Cycle 16 • Venetoclax and ibrutinib should be dosed together at the same time each day with a meal and water • Dose modification for adverse events are specified in Section 5.4.2.5 **Randomization Phase:**  *Randomization Phase– MRD-negative subjects:* *Ibrutinib* • Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression (post reintroduction when applicable) or unacceptable toxicity

	OR *Placebo* • Orally once daily matching placebo capsules (3 capsules) continuously until confirmed MRD-positive relapse, disease progression or unacceptable toxicity *Randomization Phase – MRD-positive subjects*: *Ibrutinib + venetoclax* • Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression or unacceptable toxicity plus • Orally once daily venetoclax 400 mg daily (four 100 mg tablets) *OR* *Ibrutinib* • Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression (post reintroduction when applicable) or unacceptable toxicity Reintroduction of ibrutinib or venetoclax: Upon confirmed MRD-positive relapse in MRD-negative randomized subjects or confirmed disease progression by IWCLL criteria in any randomized subjects, ibrutinib and/or venetoclax may be reintroduced. Subjects who are receiving placebo treatment, when MRD-positive relapse or disease progression are confirmed, may reintroduce oral daily ibrutinib until disease progression or unacceptable toxicity. Subjects who are receiving oral daily ibrutinib may reintroduce oral daily venetoclax. Standard TLS risk assessment, venetoclax dose ramp up, and TLS management should be employed at venetoclax reintroduction (VENCLEXTA® (venetoclax) prescribing information). **2) Fixed Duration Cohort** *Ibrutinib:* • Orally once daily ibrutinib 420 mg (3 capsules) • Single-agent lead-in for 3-cycles, then continued in combination for 12 additional cycles until completion of Cycle 15 • Dose modification for adverse events are specified in Section 5.4.1.4 *Venetoclax:* • Orally once daily venetoclax, with 5-week dose ramp up (VENCLEXTA® (venetoclax) prescribing information), to 400 mg daily, added to ongoing ibrutinib therapy starting at Cycle 4 and continuously for 12 cycles until completion of Cycle 15 • Venetoclax and ibrutinib should be dosed together at the same time each day with a meal and water

	• Dose modification for adverse events are specified in Section 5.4.2.5 NOTE: If dictated by emerging data from this study, the duration of combined ibrutinib + venetoclax treatment may be modified to ensure appropriate risk-benefit is maintained, compared to historical controls and other emerging data. Subjects with confirmed progression by IWCLL criteria after completion of the fixed duration regimen can be retreated with.continuous single agent ibrutinib, or retreatment with the ibrutinib + venetoclax fixed duration treatment regimen may be considered based on Investigator's clinical discretion and Medical Monitor's approval.
Concomitant Therapy:	Refer to Section 6 for information on concomitant therapy.

Safety Plan:	The safety of this study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. A Data Review Committee (DRC) will be organized to assess safety, tolerability, and make a recommendation regarding dosing after the Safety Run-in Period. **Safety Run-in Period:** Approximately 12 subjects will be enrolled in a Safety Run-in Period, defined as the date of first dose of ibrutinib at Cycle 1 Day 1 through the DLT evaluation period. The DLT evaluation period is defined as the 5-week venetoclax dose ramp-up in combination with ibrutinib plus an additional week of follow up. Enrollment will be held until safety is assessed by the DRC in the first 6 evaluable subjects who complete the Safety Run-in Period. Subjects' laboratory results and AEs will be reviewed by the DRC. If ≤1 of the first evaluable 6 subjects experience a DLT, the study will continue. If 2 of the first 6 evaluable subjects experience a DLT, then the DRC will evaluate safety in the next 3 evaluable subjects. If 3 or more of the 9 subjects experience DLTs, the DRC may recommend the dose of the study drug(s) to be de-escalated as per Table 1 in Section 5.2.1. The study will be deemed safe to proceed when 6–9 subjects complete the Safety Run-in Period (DLT observation period) and if <33% (≤1 of 6, or ≤2 of 9) of subjects experience a DLT. Any case of clinical TLS during the Safety Run-in Period will trigger a DRC review of that subject. Enrollment will be staggered to no more than 3 subjects per week during the Safety Run-in Period in order to minimize patient exposure and risk during this initial run in period. A follow-up DRC review will occur after all subjects in the Safety Run-in Period have either discontinued therapy and/or have completed the DLT evaluation period (venetoclax dose ramp-up plus 1-week follow-up), then DRC may make a recommendation regarding dosing. **General Safety Plan:** All subjects will be assessed for TLS risk at baseline and prior to commencement of venetoclax dosing using the previously described approach based on tumor burden (Seymour 2014), consistent with the VENCLEXTA® (venetoclax) prescribing information, and noted in Section 5.4.2.2. See Section 7.1.1.9 and Section 7.1.1.10 for TLS risk assessment and prophylaxis respectively. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns. The safety will be monitored in accordance with the Sponsor's routine Pharmacovigilance Committee procedures.

Statistical Methods and Data Analysis:	**1) MRD Cohort** Descriptive statistics and subject listings will be used to summarize the data. For continuous variables the number of observations, means, standard deviations, medians, and ranges will be reported. For discrete variables, frequencies and percentages will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided. No inferential tests will be performed for pre-randomization phase. The primary endpoint, 1-year disease-free rate in MRD-negative randomized subjects, will be tested between placebo and ibrutinib arms at a 2-sided alpha level of 0.05. Safety endpoints will be summarized descriptively based on subjects who received at least one dose of treatment. **2) Fixed Duration Cohort** Efficacy analyses will be based on the all-treated population without del17p. The 95% confidence interval will be estimated for complete response rate and MRD-negative response rate. Duration of response, PFS, and OS will be summarized using the Kaplan-Meier method. Summaries based on all-treated population will also be presented. Safety endpoints will be summarized descriptively based on subjects who received at least one dose of treatment.

Sample Size Determination	**1) MRD Cohort** The study cohort will be powered based on the Randomization Phase primary endpoint of 1-year disease-free rate in MRD-negative randomized subjects (ibrutinib vs placebo). The total sample size will be based on both MRD-negative response rate from the Pre-randomization Phase and the sample size assumption from the Randomization Phase. Sixty randomized subjects with confirmed MRD-negative status will provide approximately 80% power to detect a 30% improvement in the 1-year disease-free rate, assuming the 1-year disease-free rate is 60% for the control (placebo) arm, at a 2-sided significance level of 0.05. Assuming a 40% MRD-negative response rate for the ibrutinib and venetoclax combination therapy in the Pre-randomization Phase, 150 subjects will be enrolled in the Pre-randomization Phase in order to have 60 subjects achieving a confirmed MRD-negative response and to be randomized. The final sample size may be adjusted based on an early assessment of the MRD-negative response rate among the first 30 subjects who complete 9 cycles of treatment in Pre-randomization Phase (See section 3.1.1). **2) Fixed Duration Cohort** Assuming the CR rate for ibrutinib + venetoclax is 50%, 125 subjects without del 17p will provide 83% power to ensure the rate is > 37% at 1-side alpha 0.025. A CR rate of 50% would represent a significant improvement compared to the CR rate seen with the fixed duration combination of bendamustine + rituximab (31%) and would demonstrate a clinically meaningful improvement over the CR rate seen with the most effective standard of care fixed duration regimen fludarabine, cyclophosphamide and rituximab (40%) which were obtained in the CLL10 study, which included only patients without del 17p (Eichhorst 2016).

ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia cells
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BM	bone marrow
BMA	bone marrow aspirate
BR	bendamustine + rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CRR	complete response rate
CRi	Complete response with incomplete bone marrow recovery
CrCl	creatinine clearance
CRF	case report form (paper or electronic as appropriate for this study)
CT	Computed Tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CTLS	clinical tumor lysis syndrome
CYP	cytochrome P450
del17p	deletion of the short arm of chromosome 17
DFS	Disease-free survival
DLBCL	diffuse large B-cell lymphomas
DLT	dose limiting toxicity
DOR	Duration of Response
DRC	Data Review Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EDC	electronic data capture
FCR	fludarabine, cyclophosphamide and rituximab
FD	Fixed Duration
FDA	Food and Drug Administration
FISH	fluorescense *in situ* hybridization
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IAC	Interim Analysis Committee
IB	Investigator's Brochure

IBR	Ibrutinib
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGHV	immunoglobulin heavy-chain variable region
ILD	interstitial lung disease
INR	International normal ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITT	Intention-to treat
I+V	ibrutinib plus venetoclax combination
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	lactate dehydrogenase
LN	lymph node
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	Magnetic Resonance Imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PCR	polymerase chain reaction
PD	progressive disease or disease progression
PFS	progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	Oral
PR	partial response
PRL	PR with lymphocytosis
aPTT	activated partial thromboplastin time
PT	prothrombin time
QD	once daily
QTc	QT interval corrected for heart rate
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
REB	Research Ethics Board
RS	Richter's syndrome
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome

ULN	upper limit of normal
USPI	United States package insert
VEN	Venetoclax
WM	Waldenström's macroglobulinemia

1. BACKGROUND

1.1. Disease/Histology

1.1.1. Disease Background

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 (SEER 2016).

The predominantly older 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) (Müller-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).

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). In addition to del17p/TP53, immunoglobulin heavy-chain variable (IGHV) gene somatic hypermutation status (IGHV-MS) is an important prognostic factor. Unmutated IGHV, which occurs in about 40-50% of CLL patients, is predictive for time to first treatment (Wierda 2011) and is associated with a worse survival (Bulian 2012, Pflug 2014).

1.1.2. Current Treatment Options in Previously Untreated CLL

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 (CIT) combination of fludarabine, cyclophosphamide and rituximab (FCR). FCR resulted in significant improvement in PFS and OS compared with fludarabine and cyclophosphamide alone, with a hazard ratio for progression of 0.51 (95% CI: 0.39, 0.67) for patients less than 70 years of age (N = 736) (Hallek 2010, Casak 2011). 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 FCR remains the most active regimen and regarded as a standard of care for young fit first line patients (Hillmen 2010).

Despite the improved efficacy of CIT, only 40-45% of patients treated with these approaches currently achieve a complete response (CR) and many patients (including those achieving CR) eventually relapse (Hallek 2010, Tam 2008, Kay 2007, Fischer 2016). In some patients, CIT has resulted in attainment of undetectable minimal residual disease (MRD), defined as detection of <1 CLL cell in 10,000 normal leukocytes by either polymerase chain reaction assay or 4 color flow cytometry. These MRD-negative remissions are associated with longer PFS and OS (Bottcher 2012, Strati 2014), however, only 43-49% of patients who are evaluated for MRD (27-43 % of ITT patients) are able to achieve MRD-negative remissions (Bottcher 2012, Strati 2014). Additionally, MRD-negative remissions are achieved in a lower percent of unmutated vs mutated IGHV patients post CIT (33% vs 50.7% respectively of those evaluated) (Thompson 2016). Although some patients derive significant benefit from CIT, fludarabine based CIT regimens result in substantial toxicity including profound immunosuppression, prolonged cytopenias (which can restrict salvage therapy options at the time of recurrence), and a 5-10% risk of therapy-related myelodysplasia (MDS) (Tam 2008, Keating 2005, Ferrajoli 2005). These toxicities are problematic since most CLL patients are >age 50 at diagnosis and many patients have comorbidities that limit their ability to receive CIT (Hallek 2013). Even among younger fit CLL patients, >25% are unable to tolerate FCR-based CIT, Phase 3 trial indicate that 56% of patients experience Grade 3-4 myelosuppression, 25% infectious complication, 47% require dose reductions, and >25% of patients are unable to complete the intended 6 cycles of FCR induction even with dose reductions (Hallek). While FCR has been a major advance in the CLL treatment, it is associated with significant toxicity that limits the benefit of this approach for many patients.

Recently, in the RESONATE-2 randomized trial, single-agent ibrutinib (administered daily until progression or unacceptable toxicity) demonstrated superior PFS and OS compared to chlorambucil in previously untreated CLL patients (Burger 2015). At 18.4 months of follow up, ibrutinib significantly reduced the risk of progression or death by 84% compared to chlorambucil

(median PFS not reached vs. 18.9 months respectively; hazard ratio, 0.16; P<0.001). Notably, the 18 month PFS was 89% in both unmutated and mutated IGHV subgroups treated with ibrutinib, compared to 47% and 51% in these respective subgroups treated with chlorambucil. Additionally, ibrutinib reduced the relative risk of death by 84% (hazard ratio, 0.16; P = 0.001). The overall response rate was higher with ibrutinib compared with chlorambucil (86% vs. 35%, P<0.001), and the rates of sustained increases from baseline values in the hemoglobin and platelet levels were higher with ibrutinib. Adverse events of any grade that occurred in at least 20% of the patients receiving ibrutinib included diarrhea, fatigue, cough, and nausea, and were mainly Grade 1-2. At 18.4 months of follow-up, 87% of the patients in the ibrutinib group continued on therapy (Burger 2015). Ibrutinib was approved by US FDA in March 2016 based on this data for the first line treatment of CLL.

Although ibrutinib has resulted in an improvement in PFS and OS in treatment naïve patients (Burger 2015), and previously treated patients (Byrd 2014), single-agent ibrutinib has rarely demonstrated the ability to induce undetectable MRD by PCR or 4 color flow cytometry with a sensitivity of $<1x10^{-4}$. The addition of ibrutinib to bendamustine + rituximab (BR) resulted in a higher MRD-negative CR/CRi rate in previously treated CLL patients compared to placebo + BR (4.2% vs 1.5% by IRC; 9.3% vs 2.4% by investigator assessment) (Chanan-Khan 2016). The MRD-negative rate reached a plateau 9 months after completion of placebo+BR, however increased overtime with continued ibrutinib therapy (Fraser 2016).

Phase 1 data of single-agent venetoclax in relapsed CLL or SLL patients (n=56 in the dose escalation cohort and n=60 in the expansion cohort) demonstrated reduction of CLL burden in the blood, lymph nodes and bone marrow, with a pooled overall response rate (ORR) of 79% including 20% CR/CRi (Roberts 2015). The response rate did not differ by risk factors, including deletion 17p CLL, resistance to fludarabine, unmutated IGHV, or bulky disease. Importantly, 35% (6/17) of those patients who achieved CR and were evaluated for MRD in bone marrow became MRD-negative. In the dose-escalation cohort, tumor lysis syndrome (TLS) occurred in 10 of 56 patients (18%), including clinical TLS in 3 patients and laboratory TLS in 7 patients. In the expansion cohort, patients received an extended step-wise dose ramp-up schedule with TLS prophylaxis and hospitalization according to their level of TLS risk, resulting in no cases of clinical TLS and reduced laboratory TLS. Adverse event of any grade that occurred in at least 20% of patients included diarrhea, upper respiratory tract infection, nausea, neutropenia, fatigue, cough, pyrexia, anemia, headache, constipation and thrombocytopenia. Phase 2 data of single-agent venetoclax in ultra high-risk relapsed/refractory del17p CLL (N=107) demonstrated a 79% ORR including 7.5% CR/CRi (Stilgenbauer 2015). No detectable MRD was observed in peripheral blood in 21% of responders with MRD assessments (17% of whole cohort). Venetoclax received accelerated approval from US FDA in April 2016 based on this data for patients with CLL with 17p deletion who have received at least one prior therapy. Venetoclax received conditional approval from the European Commissions in December 2016 for the treatment of patients with CLL in the presence of 17p deletion or *TP53* mutation in adult patient who are unsuitable or have failed a B-cell receptor pathway inhibitor, as well as for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both

chemo-immunotherapy and a B-cell receptor pathway inhibitor. Venetoclax, both as a single agent and in combination with other therapeutic agents, continues to show promising efficacy in oncology subject populations. The ORR in subjects with CLL/SLL was 74% (IRC-assessed) and 74% (investigator-assessed) for single-agent venetoclax (Study M12-175 and Study M13-982, respectively), ranged from 67% to 57% for subjects with ibrutinib- or idelalisib-resistant CLL in Study M14-032, and was 86% for venetoclax administered in combination with rituximab (Study M13-365).

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 patients with B-cell malignancies.

Ibrutinib has been approved in many regions, including the (United States) US and (European Union) 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), patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and for patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic 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 BCR 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 Pharmacology 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 malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [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 the most up to date and most comprehensive safety information regarding ibrutinib, please refer to the current 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 from a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

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

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

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

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 are briefly 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).

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

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

[a]Source is Table 10 of IB (v10), [b]Source is Table 12 of IB (v10), [c]Source is Table 13 of IB (v10).

1.2.4. Risks

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

1.2.4.1. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.1.4).

1.2.4.2. Bleeding-related Events

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

or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Ibrutinib should be held at least 3 to 7 days pre-surgery and at least 3 to 7 days post-surgery depending upon the type of surgery and risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.2.4 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.

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 and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain adequate fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4.1.4).

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) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.2.4.6. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.1.4).

1.2.4.7. 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 5.4.1.5.

1.2.4.8. 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 66% of subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings (Hallek 2008, Hallek 2012, Hallek 2013). The onset of isolated lymphocytosis occurs during the first month of ibrutinib therapy and resolves by a median of 14 weeks (range, 0.1 to 104 weeks). When ibrutinib was administered with chemoimmunotherapy (bendamustine + rituximab [BR]), lymphocytosis was 7% with ibrutinib + BR versus 6% with placebo + BR.

1.2.4.9. Non-melanoma Skin Cancer

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

1.2.4.10. 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.

1.2.4.11. 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.

1.2.4.12. 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. Venetoclax Overview

Venetoclax (VENCLEXTA™) is a potent, orally administered inhibitor of B-cell lymphoma 2 (BCL-2) co-developed by AbbVie Inc and Genentech Inc for the treatment of B-cell malignancies.

Venetoclax is approved in the US for the treatment of patients with CLL or SLL, with or without 17p deletion, who have received at least one prior therapy. Venetoclax is also approved in the EU and other regions for the treatment of adult patients with CLL when used as monotherapy the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable or have failed a B-cell receptor pathway inhibitor or for the treatment of CLL in the absence of 17p deletion of TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor, and in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy. Venetoclax has also been approved in the US in combination with azacitidine, or decitabine, or low-dose cytarabine to treat adults with newly-diagnosed acute myeloid leukemia (AML) who are 75 years of age or older, or have other medical conditions that prevent the use of standard chemotherapy.

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL) where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains (Willis 2003, Cory 2002, Borner 2003, Cory 2003). Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2 (Cimmino 2005, Calin 2008).

Venetoclax (also known as ABT-199) is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity (K_i <0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L and Bcl-w (>4,000-fold and >2,000- to >20,000-fold lower affinity than to Bcl-2, respectively) (Souers 2013). Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines (venetoclax IB). Importantly, venetoclax inhibition of Bcl-2 is independent of p53 activity.

1.3.1. Summary of Nonclinical Data

In vitro, venetoclax demonstrated broad cell killing activity against patient-derived CLL and acute myeloid leukemia (AML) cells, and a variety of lymphoma and leukemia cell lines including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), AMLs, and multiple myeloma cell lines. Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. A detailed discussion of the non-clinical toxicology, metabolism, and pharmacology can be found in the venetoclax IB.

1.3.2. Summary of Venetoclax Clinical Data

1.3.2.1. Clinical Pharmacokinetics

Following multiple oral administrations under fed conditions, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Food can increase venetoclax exposure (3.4-fold with a low-fat meal and 5.1- to 5.3-fold with a high-fat meal). Venetoclax should be administered with a meal. The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4/5. Less than 0.1% of venetoclax is excreted renally. Venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl <30 mL/min) or subjects on dialysis. Venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function based on the NCI Organ Dysfunction Working Group criteria. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 times ULN. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment.

Based on preliminary data from this combination study of ibrutinib and venetoclax in CLL (PCYC-1142-CA), venetoclax exposure (AUC) at 400 mg QD appears to be ~1.6-fold higher when co-administered with ibrutinib at 420 mg QD (N = 32), compared to historic venetoclax single agent exposure. Ibrutinib exposure was similar prior to, and in combination with venetoclax administration. To date, no new safety signals have been identified.

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

1.3.2.2. Summary of Clinical Safety

Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

As of 28 November 2016, and version 8 of the Investigator's Brochure, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 2759 subjects have

been exposed to at least 1 dose of venetoclax in the oncology and immunology development programs. A total of 2534 oncology subjects have data available in AbbVie and Genentech/Roche studies as of 28 November 2016. Of these 2534, there are 1435 subjects with CLL/ SLL, 626 subjects with NHL, 178 subjects with MM, 295 with AML. An additional 127 subjects are healthy volunteers. A total of 663 oncology subjects received the drug as monotherapy, 1871 have received the drug in combination with other therapies, and 1 subject received venetoclax as a single dose in a drug-drug interaction study and did not re-enroll into a subsequent monotherapy study. Additionally, 98 subjects have been exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093, as of 28 November 2016.

Of the 1435 subjects with CLL/SLL that have been treated in the venetoclax oncology clinical program: 416 patients have received venetoclax monotherapy and 1019 have received venetoclax in combination with other agents including rituximab, obinutuzumab, and bendamustine.

The safety profile of venetoclax was similar across CLL subjects, including subjects with 17p del or *TP53* mutation and subjects who have failed prior B-cell receptor inhibitors (BCRi), such as ibrutinib and idelalisib. The most common adverse events (incidence >20%) reported for all subjects in CLL/SLL monotherapy studies (N=410) were diarrhea (42.2%), neutropenia (41.0%), nausea (40.2%), fatigue (30.5%), anemia (28.8%), upper respiratory tract infection (27.3%), and thrombocytopenia (20.7%). The most common Grade 3 and above adverse events were neutropenia (36.8%), anemia (15.6%), and thrombocytopenia (13.4%). The most common serious adverse events were pneumonia (6.8%), malignant neoplasm progression (5.9%), and febrile neutropenia (5.4%). The safety profile in combination studies (N=1019) is consistent with that observed in monotherapy studies and combination backbone regimens.

Additional safety and efficacy data are described in detail in the venetoclax IB.

1.3.3. Risks

1.3.3.1. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with CLL. Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, have occurred in previously treated CLL patients with high tumor burden when treated with venetoclax. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with relapsed/refractory CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. The starting dose was reduced to 50 mg and prophylaxis and monitoring reduced, with 3-week ramp-up. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a ramp-up period of 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy, indicated a marked

reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or non-serious event of clinical TLS (CTLS) or had study treatment discontinued because of TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing, especially with a higher initial dose of venetoclax, as well as being greater in subjects with a large tumor burden.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk increases (see Section 5.4.2.2 for Prophylaxis and Management of TLS).

1.3.3.2. Neutropenia

Grade 3 or 4 neutropenia occurred in 41% (98/240) of patients treated with venetoclax in the pivotal previously treated CLL 17p deletion study. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (eg, G-CSF).

1.3.3.3. Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Advise patients that vaccinations may be less effective.

1.4. Study Rationale

Despite the impressive survival efficacy (90% PFS at 18 months [Burger 2015]; 94.7% 2-year survival estimate [IMBRUVICA USPI]) and safety results with single-agent ibrutinib in the randomized Phase 3 RESONATE-2 study in previously untreated CLL patients, complete responses remain low (Burger 2015, IMBRUVICA® USPI), and broader questions remain regarding the optimal duration of ibrutinib therapy. This is particularly relevant among younger patients who may not wish to continue therapy indefinitely or in those seeking a drug holiday. In such patients, an all oral truncated combination regimen approach with the ability to induce deep and durable remissions would be desirable.

Pre-clinical studies support the combination of ibrutinib with venetoclax, and suggest potential enhanced activity vs. each agent alone. Ex vivo experiments in ibrutinib treated CLL patients

demonstrated that BCL2 expression remains strong throughout the 6 months of ibrutinib treatment (Rawstron 2015). In vitro experiments on previously untreated CLL patient samples suggest that ibrutinib increases the dependence of CLL cells on BCL-2 (Deng 2015). Additionally, ex vivo experiments on CLL cells from patients demonstrated that ibrutinib exposure retained sensitivity to venetoclax, that venetoclax induced potent CLL cell death (median 62% at week 4) in patients being treated with ibrutinib, and that cytotoxicity was greater than each agent alone (Cervantes-Gomez 2015).

As of the time of protocol design, in the relapsed CLL setting, single-agent venetoclax had induced a 79% ORR, including 20% CR in previously treated CLL patients in a Phase 1 study. Of the CR patients evaluated for minimal residual disease (MRD) in bone marrow, 35% (or 5% of the total study population) became MRD-negative via flow cytometry (Roberts 2015). In a Phase 2 study in patients with relapsed deletion 17p CLL, the IRC assessed response was 69% including 7.5% CR/CRi, and MRD-negativity in peripheral blood was achieved in 21% (18/85) of responders (Stilgenbauer 2015). MRD-negative response in the bone marrow was achieved in 53% (26/49) of patients, including 75% (15/20) of patients who achieved CR or CRi with the combination of venetoclax plus rituximab in previously treated CLL patients (Ma 2015). Clinical remission has been maintained after venetoclax discontinuation in six patients who achieved MRD-negative CR, with a median follow up of 15 months off therapy (range 4-24 months). Despite impressive response rates and the ability to achieve MRD-negativity in some patients, PFS has remains relatively short with single-agent venetoclax (66% - 72% at 12-15 months) and combination therapy may afford a better long-term outcome (84% PFS at 24 months with rituximab in the relapsed setting).

At the time of protocol design, there was little data with venetoclax in treatment naïve CLL. Safety run-in results for the ongoing CLL14 study of venetoclax with obinutuzumab demonstrated that the combination was tolerable with 15% of patients developing Grade 3-4 infusion related reactions with obinutuzumab, and 15% developing Grade 3-4 laboratory tumors lysis syndrome (TLS) (Fischer 2015). As infusion-related reactions are not a concern with ibrutinib, an ibrutinib lead-in to debulk tumor, followed by the combination of ibrutinib with venetoclax may afford better tolerability. The combination of ibrutinib with venetoclax may be an effective strategy to achieve deep and durable MRD-negative responses in treatment naïve CLL patients. The German CLL Study Group is also planning a study of venetoclax, ibrutinib, plus obinutuzumab (CLL2-GiVe, NCT02758665) in physically fit previously untreated CLL.

At the time of protocol design, PCYC-1142-CA was the first clinical trial to study the combination of ibrutinib + venetoclax (I+V) in subjects with treatment naïve CLL, therefore a Safety Run-in Period will be instituted to evaluate safety and tolerability of the combination, and determination of the recommended doses. Additionally, venetoclax will be introduced after 3 cycles (1 cycle = 28 days) of single-agent ibrutinib lead-in, representing the period after the ibrutinib-induced lymphocytosis peak and where most treated subjects will have experienced significant reduction in lymphadenopathy. Utilizing the previously published calculations to determine TLS risk categories for venetoclax based on tumor burden (Seymour 2014, Appendix

H as noted in the VENCLEXTA® (venetoclax) prescribing information, TLS risk at baseline and at first assessment were calculated utilizing CT scans after 4 cycles of ibrutinib from the RESONATE-2 ibrutinib treatment naïve Phase 3 CLL study (N=135) and after 2 cycles of ibrutinib in PCYC-1102 Phase 1b/2 treatment naïve cohorts (N=27).The percent of subjects at high or moderate-risk for tumor lysis syndrome (TLS) at baseline was reduced from 81% to 59% after 2-4 cycles of ibrutinib, and the percent of subjects at high-risk for TLS at baseline was reduced from 28% to 7% after 2-4 cycles of ibrutinib. Due to transient increase in ALC, a minority (5%) of patients increased from low to medium risk at first assessment, however no patients increased from low or medium to high risk. For patients with treatment naïve CLL or SLL with CrCl <80 mL/min, 36% (25/69) with medium TLS risk at baseline were reduced to low risk by first assessment and 26% (10/30) with high TLS risk at baseline were reduced to low risk by first assessment, further reducing the overall percent of patients requiring hospitalization (Wierda 2017). Therefore, employing a 3-cycle ibrutinib lead-in and sequencing ibrutinib prior to venetoclax should provide tumor debulking and convert higher TLS risk subjects to lower TLS risk subjects.

At the time of protocol design, preliminary clinical data from an ongoing investigator-initiated study of the combination of ibrutinib and venetoclax (I+V) in subjects with high-risk, relapsed/refractory CLL (CLARITY Study, ISCRTN: 13751862) indicated that the combination is highly effective, with rapid clearance of disease and an acceptable safety profile (presented at the American Society of Hematology [ASH] Annual Meeting, December 2017; Hillmen 2017). In this study, the ibrutinib lead-in is 8 weeks, after which the ibrutinib + venetoclax (I+V) combination starts. Treatment continues for a period of 14 to 26 months, depending on MRD-negative status. Median baseline CLL burden in PB, as assessed by the MRD assay in the first 46 subjects, was 54.5 $x10^9$/L. This declined down to 0.001 $x10^9$/L in the 37 subjects who have completed 8 months of therapy (including 6 months of the combination I+V). All evaluable subjects at the 8-month time point (38/38) had an objective response (100% ORR), 18/38 (47%) achieved CR or CRi. Peripheral blood was MRD negative in 15/38 (37%) and BM was MRD negative in 12/38 (32%). The combination of I+V was reported to have an acceptable safety profile, with most AEs being Grade 1 or 2. Two biochemical TLS events were reported, but only 1 case met the definition of laboratory TLS. Dosing of venetoclax was interrupted until the biochemical abnormalities resolved and the patients subsequently escalated to 400 mg/day of venetoclax.

At the time of protocol design, the Phase 2 investigator-initiated study conducted at the University of Texas MD Anderson Cancer Center (Study NCT02756897) is investigating the combination of I+V in subjects with relapsed/refractory CLL (n=33) and in treatment naive (n=39) subjects with CLL with at least 1 of the following high-risk features: del17p, mutated TP53, del11q, unmutated IGHV, or ≥ 65 years of age. Subjects are treated with single agent ibrutinib (420 mg daily) for 3 months, followed by addition of venetoclax. As presented at the American Society of Hematology [ASH] Annual Meeting, December 2017 (Jain 2017), three months of single agent ibrutinib therapy reduced the TLS risk category in 31 of 61 evaluable subjects (51%). In the 16 subjects with relapsed/refractory CLL who completed at least 6 months

of combination therapy, 100% had a response (69% CR/CRi), and 13% were MRD-negative in BM. In the 20 subjects with treatment naive, high-risk CLL who completed at least 6 months of the combination, 100% had a response (75% CR/CRi), and 45% were MRD-negative in BM. One patient had laboratory TLS, none had clinical TLS.

Addition of a Fixed Duration cohort to this study is based upon promising preliminary response data (CR, ORR, MRD negative rates) for ibrutinib-venetoclax combination therapy from PCYC, investigator-sponsored trials, and other investigator-led studies. After 9 cycles of therapy (6 cycles of I+V combination), 5 of the first 7 subjects in the MRD cohort of this study have achieved MRD-negativity (<0.01%) in the peripheral blood with the remaining 2 subjects having only 0.01% MRD.

Together, these preliminary data indicate the combination of ibrutinib and venetoclax has the potential for use as a fixed duration regimen. The primary objective of this study is to demonstrate a high CR rate in reference to historical data with fixed duration chemo-immunotherapy, tested in a similar population. This fixed duration I+V regimen would be of value for several reasons, particularly given the barriers to MRD testing in the community and the acceptance of fixed duration standard chemoimmunotherapy regimens. If effective, the fixed duration I+V therapy would also provide benefit to the patient as well as economic benefits given the shorter treatment administration, alleviating the need for long-term dose adherence, and providing treatment holidays with the option for treatment following progression.

MRD-negative remission is associated with superior PFS and OS with chemoimmunotherapy (CIT) in patients with CLL (Thompson 2016), however whether confirmed MRD-negative remissions with novel non-CIT regimens will also translate into a survival benefit is not yet known. Additionally, it will be important to understand if extended treatment with ibrutinib in patients without confirmed MRD negative remissions after 15 cycles can lead to deeper responses and attainment of MRD-negativity. This Phase 2 placebo-controlled study will investigate the activity of ibrutinib plus venetoclax in treatment-naive CLL subjects by assessing the ability to achieve complete clinical response, MRD-negative response, and the durability of response in the setting of ibrutinib discontinuation.

2. STUDY OBJECTIVE

2.1. Primary Objective

MRD Cohort

- To evaluate if discontinuing ibrutinib, in the setting of a confirmed MRD-negative response with the combination of ibrutinib + venetoclax (I+V), allows for a treatment holiday as assessed by 1-year disease-free survival. 1-year disease-free survival is defined as continued MRD-negative response without progression or death at least one year after randomization.

Fixed Duration Cohort

- To evaluate the depth of response with the combination of ibrutinib + venetoclax (I+V) administered for a fixed duration of therapy by assessment of complete response (CR/CRi) rate.

2.2. Secondary Objective(s)

2.2.1. MRD Cohort

- Minimal Residual Disease (MRD) - negative rate
- Overall response rate (ORR)
- Complete response rate (Complete Response [CR], and CR with incomplete marrow recovery [CRi])
- Duration of response (DOR)
- Tumor Lysis Syndrome (TLS) risk reduction
- Progression free survival (PFS)
- Overall survival (OS)
- Pharmacokinetics of ibrutinib and venetoclax when dosed in combination
- Safety and tolerability

2.2.2. Fixed Duration Cohort

- Duration of Response (DOR)
- Minimal Residual Disease (MRD)-negative rate
- Overall response rate (ORR)
- Tumor Lysis Syndrome (TLS) risk reduction
- Progression free survival (PFS)
- Overall survival (OS)
- Safety and tolerability

2.3. MRD Cohort Exploratory Objectives

- [redacted]

2.4. FD Cohort Exploratory Objective

- [redacted]

3. STUDY DESIGN

3.1. Overview of Study Design

This is a multicenter, 2-cohort Phase 2 study assessing both MRD-guided discontinuation and fixed duration therapy with the combination of ibrutinib + venetoclax in subjects with treatment-naïve CLL or SLL.

The MRD cohort consists of a pre-randomization phase (combination treatment), an MRD-guided randomization phase which includes reintroduction of therapy, and post-PD follow-up phase.

The Fixed Duration cohort is an open label, 1 arm cohort of ibrutinib + venetoclax combination therapy for a fixed duration.

All subjects who discontinue treatment in the absence of disease progression will remain on study until confirmed disease progression or until study closure. All subjects who discontinue for disease progression will be followed for survival and subsequent anti-cancer therapies.

Investigator assessment of disease overall response and progression will be based upon IWCLL criteria with the modification that isolated treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will **not** be considered PD (Hallek 2008, Hallek 2012, Hallek 2013, Cheson 2012). The Investigator will evaluate sites of disease by radiological imaging, physical examination or other procedures as necessary, review of hematology 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.

Imaging will be collected and stored centrally. Assessment of efficacy may be confirmed based on evaluation by an Independent Review Committee (IRC). Detailed procedures will be described in a separate charter.

For the MRD cohort, the primary analysis of the randomized phase will be performed at the point that all randomized subjects have had the opportunity to complete at least 12 cycles of randomized treatment or follow-up. All safety and efficacy endpoints will be analyzed at the time of the primary analysis. After the primary analysis, the Sponsor may elect to discontinue follow-up of specific MRD cohort treatment arms on PCYC-1142-CA. Subjects who are continuing on ibrutinib at time of study arm closure may be offered a separate extension study to continue ibrutinib.

For the FD cohort, the primary analysis will be performed when a clinically meaningful evaluation of durable CR rate (12 months or longer) can be assessed in the study population. FD Cohort subjects will be followed for approximately 5 years. All subjects who are continuing on

ibrutinib at the time of FD cohort study closure may be offered a separate extension study to continue ibrutinib.

The clinical study report for the study will be generated once the primary analyses of both the MRD cohort and FD cohorts are completed.

The rationale for the study concept is provided in Section 1.4.

Details of the sequentially designed and enrolled cohorts, MRD cohort and Fixed Duration cohort, are below.

3.1.1. MRD Cohort: Pre-Randomization Phase

Approximately 150 subjects will be enrolled into this phase. The subjects will receive single-agent ibrutinib for 3 cycles (1 cycle = 28 days) followed by ibrutinib + venetoclax combination treatment for at least12 cycles.

The safety of ibrutinib + venetoclax combination therapy will be assessed by a Data Review Committee (DRC). Approximately 12 subjects will be enrolled in a Safety Run-in Period, defined as the date of first dose of ibrutinib at Cycle 1 Day 1 through the DLT evaluation period. The DLT evaluation period is defined as the 5-week venetoclax dose ramp up in combination with ibrutinib, plus an additional week of follow up (6 weeks total). Enrollment will then be held until safety is assessed by the DRC in the first 6 evaluable subjects who complete the Safety Run-in Period. Subjects' laboratory results and AEs will be reviewed by the DRC. If ≤1 of the first 6 evaluable subjects experience a DLT, the study will continue. If 2 of the first 6 evaluable subjects experience a DLT, then the DRC will evaluate safety in the next 3 evaluable subjects (9 subjects total). The study will be deemed safe to proceed when 6–9 subjects complete the Safety Run-in Period (DLT evaluation period) and if <33% (≤1 of 6, or ≤2 of 9) of subjects experience a DLT. The DRC will meet and review safety data after all 12 subjects in the Safety Run-in Period have either discontinued therapy and/or have completed the DLT evaluation period (venetoclax dose ramp up plus 1 week follow up), then DRC may make a recommendation regarding dosing.

Subjects will be assessed for MRD status in peripheral blood every 3 cycles on the combination therapy starting after completion of Cycle 6 (C7D1), and in bone marrow aspirate after completion of Cycle 15 (C16D1). MRD assessment will be performed using flow cytometry with a sensitivity of $\geq 10^{-4}$. An early assessment of the MRD-negative response rate of the combination therapy will be assessed among the first 30 subjects who complete 9 cycles of treatment. The sample size may be adjusted accordingly based on this early assessment to adequately power the Randomization Phase primary endpoint.

MRD-negative response for randomization purposes must be confirmed serially over at least 3 cycles, and is required to demonstrate negativity in both bone marrow and peripheral blood.

Subjects who complete at least 12 cycles of combination therapy and subjects who discontinue venetoclax in the Pre-randomization Phase due to reasons other than PD (but continue on ibrutinib single agent treatment and achieve confirmed MRD-negativity by the end of Cycle 16) are eligible for randomization. Subjects who have discontinued ibrutinib and subjects that are MRD-positive and have discontinued venetoclax are not eligible to be randomized but will continue the tolerated open label treatment until PD or unacceptable toxicity.

3.1.2. MRD Cohort: Randomization Phase (Including Re-introduction Period)

Eligible subjects will be randomized in a 1:1 ratio based on their MRD status (see below). Subjects will be stratified by immunoglobulin heavy-chain variable region (IGHV) status in each randomization strata.

Randomization Phase - MRD-negative subjects (Double-blind):

Eligible subjects who achieve a confirmed MRD-negative response will be randomized to receive blinded treatment of ibrutinib (venetoclax discontinued) vs placebo (ibrutinib and venetoclax discontinued). The randomization will be stratified by IGHV status. Subjects will be assessed for disease-free survival as measured by continued MRD-negative response without progression or death at least 1 year after randomization. MRD status will be evaluated every 3 cycles in PB. MRD should also be reassessed in BM aspirate after an additional 12 cycles.

Randomization Phase - MRD-positive subjects (Open-label):

Those subjects who do not achieve a confirmed MRD-negative response (MRD-positive) after 12 cycles of the combination will be randomized to receive open label treatment of I+V vs ibrutinib alone (venetoclax discontinued). The randomization will be stratified by immunoglobulin heavy-chain variable region (IGHV) status. Subjects will subsequently be assessed for MRD-negative response. MRD status will be evaluated every 3 cycles in peripheral blood. MRD should also be reassessed in BM aspirate after an additional 12 cycles and at any time in subjects who become MRD negative in PB. For subjects receiving I+V, venetoclax can be administered for up to approximately 2 years per treatment course, until PD or unacceptable toxicity, or until this arm's study closure, whichever is earlier. Subjects who are continuing on ibrutinib at time of study arm closure may be offered a separate extension study to continue ibrutinib.

Reintroduction of therapy**:**

Subjects who wish to reintroduce therapy for MRD-positive relapse (see definition in Section 7.2.1.4.2) and/or for disease progression must undergo a CT scan for re-staging (unless previously done ≤2 months prior to reintroduction). For MRD-negative and MRD-positive subjects who reintroduce venetoclax, venetoclax can be administered for up to 2 years per treatment course, until PD or unacceptable toxicity, or until these arms' study closure, whichever is earlier. Subjects who are continuing on ibrutinib at time of study arm closure may be offered a separate extension study to continue ibrutinib. Any non-study therapy should only be administered following documented IWCLL confirmed PD.

MRD-negative randomized subjects who experience confirmed MRD-positive relapse and/or confirmed disease progression may have their randomization unblinded, and receive reintroduced therapy as follows:

Placebo subjects: Subjects on the placebo arm will be offered the opportunity to reintroduce ibrutinib to assess if they can benefit from single-agent ibrutinib under the following circumstances:

- For confirmed MRD-positive relapse and/or for disease progression by IWCLL criteria, subjects will receive ibrutinib until PD or unacceptable toxicity. Ibrutinib reintroduced subjects who subsequently have confirmed disease progression by IWCLL criteria may continue ibrutinib and add venetoclax per standard dose ramp up

Ibrutinib subjects: Subjects on the ibrutinib arm will be offered the opportunity to continue ibrutinib and reintroduce venetoclax treatment under the following circumstances:

For confirmed MRD-positive relapse and/or for confirmed disease progression by IWCLL criteria, subjects can continue ibrutinib and add venetoclax per standard dose ramp up.

MRD-positive randomized subjects can receive reintroduced therapy as follows:

Ibrutinib only subjects: Subjects on the ibrutinib arm will be offered the opportunity to continue ibrutinib and reintroduce venetoclax treatment per standard dose ramp up under the following circumstances:

- For confirmed disease progression by IWCLL criteria, subjects can add venetoclax to ongoing ibrutinib
- For subjects who have confirmed disease progression and reintroduced therapy, a new baseline for response assessment will be collected and utilized for calculating time to next PD on reintroduced therapy.

3.1.3. Fixed Duration Cohort

Approximately 125 subjects without del 17p will be enrolled into this cohort sequentially after the MRD cohort. Subjects will receive 15 cycles of therapy consisting of single-agent ibrutinib for 3 cycles followed by ibrutinib + venetoclax combination treatment for 12 cycles. If emerging data from this study indicate, the duration of combined ibrutinib + venetoclax treatment may be modified to ensure appropriate risk-benefit is maintained, compared to historical controls and other emerging data.

All subjects will be assessed for MRD status in peripheral blood (PB) every 3-12 cycles starting after completion of 6 cycles (C7D1), and in bone marrow (BM) aspirate after completion of 9 cycles (C10D1) and 3 months after completion of the fixed duration Cycle 15 (ie, C19), or earlier if BM is indicated for confirmation of CR per IWCLL response criteria. MRD assessments will be performed using flow cytometry with a sensitivity (lower limit of detection) of 1 CLL cell in 10,000 leukocytes (10^{-4}).

Reintroduction of therapy

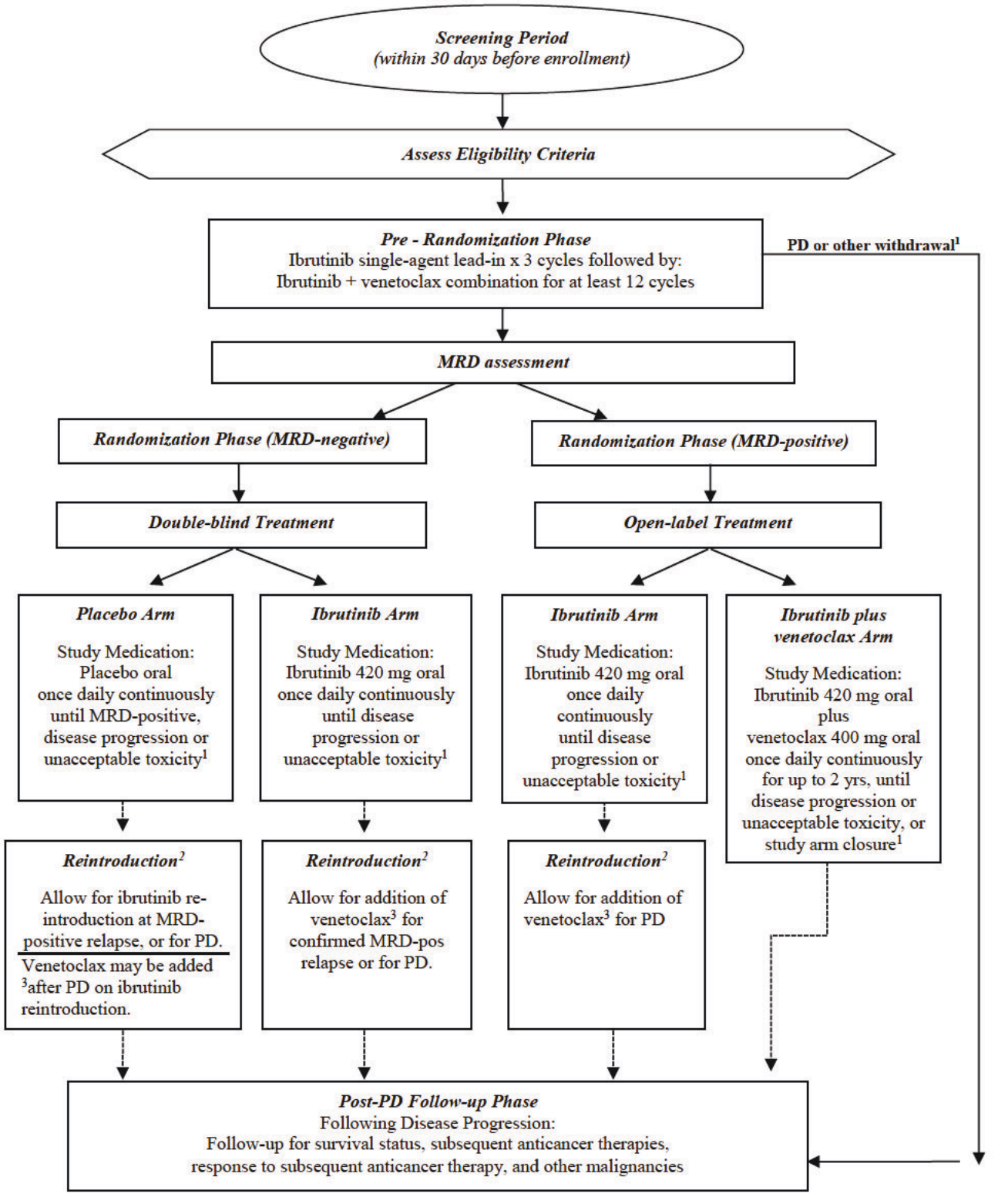
Subjects with confirmed progression per IWCLL criteria after completion of the fixed duration regimen can be retreated with continuous single agent ibrutinib until disease progression or unacceptable toxicity because it is an established standard of care for treatment of relapsed CLL. For subjects that experience durable efficacy after I+V (ie, time to progression after fixed duration regimen is completed of >2 years), the I+V fixed duration treatment regimen may be repeated based on Investigator's clinical discretion and Medical Monitor's approval. Retreatment is for 15 cycles, until PD or unacceptable toxicity, whichever is earlier.

Subjects will be followed for progression, overall survival (OS), and use of subsequent anticancer agents until study closure.

3.1.4. Post-PD Follow-Up Phase

Subjects who have confirmed disease progression by IWCLL criteria and have discontinued study treatment will be followed for survival status and subsequent anti-cancer therapy until study closure.

3.2. Study Schema; MRD Cohort

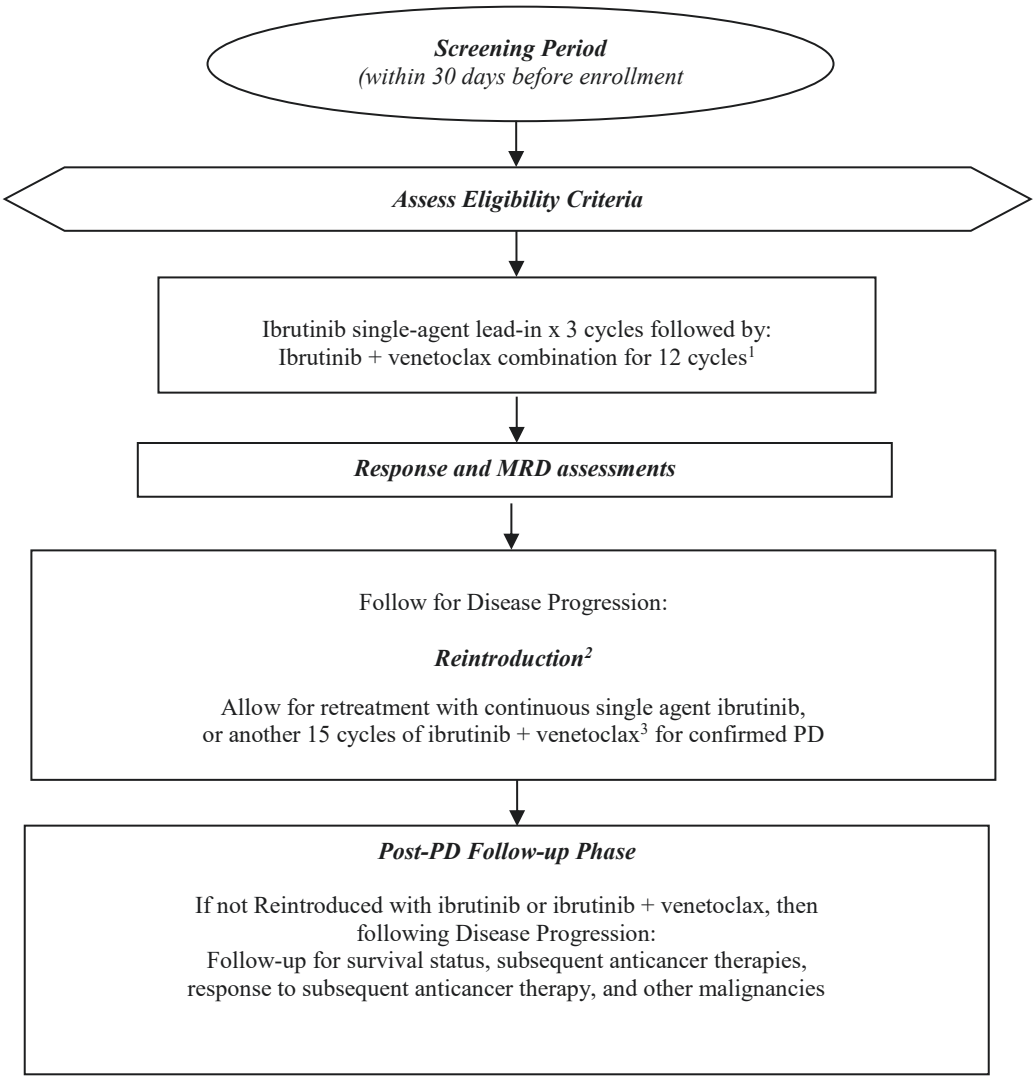


1 Subjects who discontinue treatment for reasons other than confirmed PD should continue participating in ongoing response follow-up visits until confirmed PD

2 Refer to Sections 3.1.2 and 5 3 2 for details regarding MRD cohort Reintroduction

3 Addition of venetoclax will follow the standard dose ramp up. Venetoclax for up to 2 yrs, until PD or unacceptable toxicity, or study arm closure, whichever is first

3.3. Study Schema; Fixed Duration Cohort



1 Administer 12 cycles of ibrutinib + venetoclax unless discontinue for PD or toxicity. Subjects who discontinue treatment for reasons other than confirmed PD should continue participating in ongoing response follow-up visits until confirmed PD

2 Refer to Sections 3.1.3 and 5.3.3 for details regarding FD cohort Reintroduction

3 Addition of venetoclax will follow the standard dose ramp up. Venetoclax for up to 2 yrs, until PD or unacceptable toxicity, or study arm closure, whichever is first

4. SUBJECT SELECTION

4.1. Inclusion Criteria

Prior to enrollment, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008).
2. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:
   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
   - Massive, progressive, or symptomatic splenomegaly
   - Massive nodes or progressive or symptomatic lymphadenopathy
   - Progressive lymphocytosis
   - Constitutional symptoms
3. Measurable nodal disease by computed tomography (CT).

Laboratory

4. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days (with the exception of pegylated G-CSF [pegfilgrastim] and darbopoeitin which require at least 14 days) prior to screening laboratory assessment defined as:
   - Absolute neutrophil count (ANC) >750 cells/μL (750 cells/mm^3 or 0.75 x 109/L)
   - Platelet count >30,000/μL (30,000 cells/mm^3 or 30 x 10^9/L)
   - Hemoglobin >8.0 g/dL
5. Adequate hepatic and renal function defined as:
   - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN)
   - Creatinine Clearance (CrCl) ≥60 mL/min (eg, as estimated by Cockcroft-Gault)
   - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
6. Prothrombin time (PT)/International normal ratio (INR) <1.5 x (upper limit of normal) ULN and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).

Demographic

7. Men and women ≥18 and ≤70 years of age.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Ethical/Other

9. 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 reproductive potential must have a negative serum pregnancy test upon study entry.
10. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[2], or sterilized partner) and a barrier method (eg, condom, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug. Male subjects must agree to refrain from sperm donation until 90 days after the last dose of study drug.

4.2. Exclusion Criteria

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

1. Any prior therapy (including but not limited to chemotherapy, targeted therapy, immunomodulating therapy, radiotherapy, and/or monoclonal antibody) used for treatment of CLL or SLL.
2. History of other malignancies, except:
   - 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 the treating physician
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease
3. Known or suspected history of Richter's transformation.
4. Concurrent administration of >20 mg/day of prednisone within 7 days of initiation of study drug unless indicated for prophylaxis or management of allergic reactions (eg, contrast).
5. Known hypersensitivity to one or more study drugs.
6. Known allergy to xanthine oxidase inhibitors and/or rasburicase. Subjects who are allergic to xanthine oxidase inhibitors and cannot receive rasburicase will be excluded.
7. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
8. Recent infection requiring systemic treatment that is ongoing or was completed ≤14 days before the first dose of study drug, or any uncontrolled active systemic infection.
9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).

10. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
11. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
12. Major surgery within 4 weeks of first dose of study drug.
13. 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.
14. 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 enrollment.
15. Unable to swallow capsules/tablets 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.
16. Concomitant use of warfarin or other vitamin K antagonists.
17. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix G).
18. Currently active, clinically significant hepatic impairment Child-Pugh Class B or C according to the Child Pugh classification (Appendix K).
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).
22. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia 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 treat or control the autoimmune disease.

5. TREATMENT OF SUBJECTS

MRD Cohort

5.1. Treatment Allocation and Blinding

Eligible subjects will be enrolled to a pre-randomization phase and receive open-label ibrutinib capsules and venetoclax tablets (single-agent ibrutinib for 3 cycles followed by ibrutinib + venetoclax combination treatment for at least 12 cycles). Subjects will then be randomized by

two separate schemes according to MRD status. Subjects who achieve confirmed MRD-negative response and who continue ibrutinib will be randomized to receive double blind study treatment with either placebo or ibrutinib; Subjects who do not achieve confirmed MRD-negative response and who continue both study drugs will be randomized to receive open label treatment either single-agent ibrutinib or ibrutinib + venetoclax combination treatment. In each scheme, the randomization will be in 1:1 ratio and stratified by IGHV status.

5.2. Safety Run-in Period

Approximately 12 subjects will be enrolled in a Safety Run-in Period, defined as the date of first dose of ibrutinib at Cycle 1 Day 1 through the DLT evaluation period. The DLT evaluation period is defined as the 5-week venetoclax dose ramp-up in combination with ibrutinib, plus an additional week of follow-up (6 weeks total). Enrollment will be held until safety is assessed by the DRC in the first 6 evaluable subjects who complete the Safety Run-in Period. Subjects will be considered evaluable for DLT assessment if they receive at least 85% of the combined therapy at the targeted doses during the DLT evaluation period, or if they experience a DLT after the first venetoclax dose. Subjects' laboratory results and AEs will be reviewed by the DRC. If ≤1 of the first 6 evaluable subjects experience a DLT, the study will continue. If 2 of the first 6 evaluable subjects experience a DLT, then the DRC will evaluate safety in the next 3 evaluable subjects (9 subjects total). The study will be deemed safe to proceed when 6–9 subjects complete the Safety Run-in Period and if <33% (≤1 of 6 or ≤2 of 9) of subjects experience a DLT.

Enrollment will be staggered to no more than 3 subjects per week during the Safety Run-in Period in order to minimize patient exposure and risk during this initial run in period.

All subjects will be assessed for TLS risk prior to initiation of venetoclax. See Section 7.1.1.9 and Section 7.1.1.10 for TLS risk assessment and prophylaxis respectively. Any case of clinical TLS (See Appendix H for TLS criteria) during the Safety Run-in Period will trigger a DRC review of that subject. The DRC will meet and review safety data after all subjects in the Safety Run-in Period have either discontinued therapy and/or have completed the DLT evaluation period (venetoclax dose ramp-up plus 1-week follow-up), then DRC may make a recommendation regarding dosing.

5.2.1. Dose-Limiting Toxicity (DLT)

Dose-limiting toxicities (DLT) are defined as clinical TLS per the Howard Criteria (Appendix I) or any new CTCAE Grade 3 or higher possibly related non-hematologic or Grade 4 hematologic adverse event occurring during the DLT evaluation period (defined as the 5-week venetoclax dose ramp-up plus 1-week follow-up) with the additional clarifications below (which will be considered DLTs):

Non-hematologic:

- Grade 4 diarrhea and vomiting

- Grade 3 nausea, vomiting or diarrhea despite maximum medical supportive care and persisting >3 days
- Grade 3 fatigue persisting >7 days
- Grade 3 rash lasting >7 days that does not resolve with appropriate clinical management

Hematologic (per IWCLL Criteria, Appendix L):

- Grade 4 neutropenia (ANC <500 μL) lasting for >7 days duration (irrespective of adequate growth factor support)
- Grade 4 thrombocytopenia that persists for >7 days
- Grade 3 thrombocytopenia associated with clinically significant bleeding

If 2 of the first 6 evaluable subjects experience a DLT, then the DRC will evaluate safety in the next 3 evaluable subjects. If 3 or more of the 9 subjects experience DLTs, the DRC may recommend the dose of the study drug(s) to be de-escalated as shown in Table 1. However, if DLTs occur at a lower dose of venetoclax, the DRC may recommend that the protocol be amended to adjust the venetoclax dose ramp-up (eg, starting dose or length of ramp-up). If modifications are made to the treatment schedule or dose to mitigate dose-limiting toxicity based on the number of DLTs during the Safety Run-in Period, safety data will be further assessed in an additional 6 evaluable subjects, until the DRC can make a recommendation (provides recommended doses for the combination).

Table 1. Dose De-Escalation Schedule for Safety Run-in

Dose Level	Ibrutinib Daily dose	Venetoclax (Target dose)
0	420 mg	400 mg
-1	420mg	300 mg
-2	280 mg	300 mg

If ≤1 of the first 6 subjects or ≤2 of the first 9 subjects treated with study drugs experience DLT(s), the 400-mg target dose of venetoclax will be considered safe in combination with ibrutinib and the DLT assessment at this target dose level will be considered completed.

5.2.2. Baseline TLS Assessment

All subjects will be assessed for TLS risk at baseline and prior to commencement of venetoclax dosing using the previously described approach based on tumor burden (Seymour 2014), consistent with the VENCLEXTA® (venetoclax) prescribing information and noted in Section 5.4.2.2. See Section 7.1.1.9 and Section 7.1.1.10 for TLS risk assessment and prophylaxis respectively.

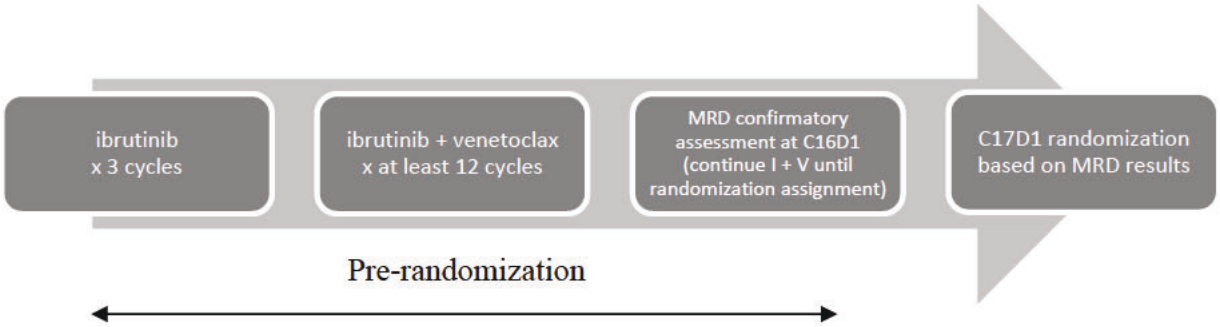
Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.

5.3. Study Treatment

5.3.1. Pre-Randomization Phase

Ibrutinib + Venetoclax Combination

In the Pre-randomization Phase, single-agent ibrutinib (420 mg/day PO) will be given as lead-in treatment for 3 cycles. Starting at Cycle 4, venetoclax will be added to the ibrutinib (420 mg/day PO) regimen continuously for at least 12 cycles until completion of Cycle 16.



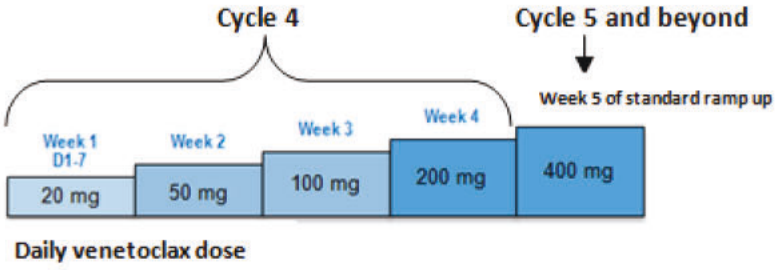
Ibrutinib:

- Orally once daily ibrutinib 420 mg (3 capsules)
- Single-agent lead-in for 3-cycles, then continued in combination for at least 12 additional cycles until completion of Cycle 16
- Dose modification for adverse events are specified in Section 5.4.1.4

Venetoclax:

- Orally once daily venetoclax, with 5-week dose ramp up, added to ongoing ibrutinib therapy starting at Cycle 4 and continued for at least 12 cycles till completion of Cycle 16, utilizing the dose ramp-up schedule in Section 5.4.2.3 and Figure 1.

Figure 1. Venetoclax Dose Ramp-up



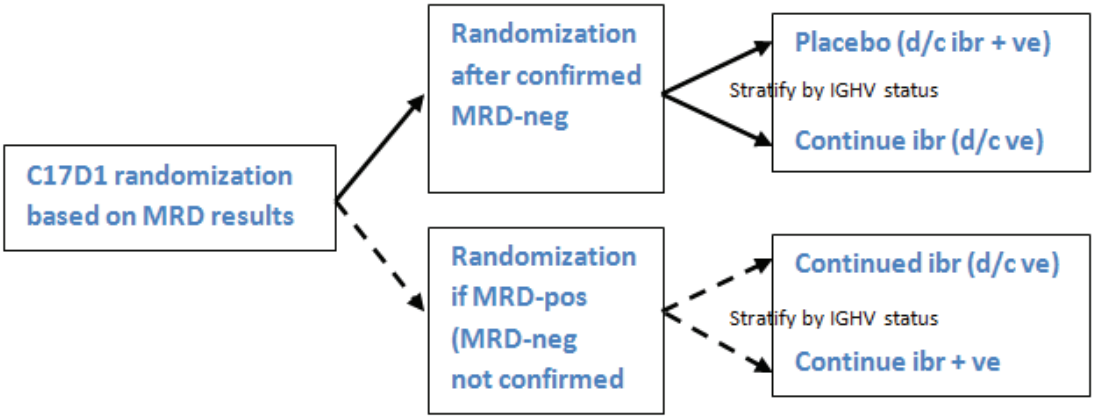
- Venetoclax and ibrutinib should be dosed together at the same time with a meal and water.

- For subjects not able to swallow all ibrutinib capsules and venetoclax pills at the same time, administration should be completed within a 60-minute window. On days of PK sample collection (C2D1 and C6D1), ibrutinib and venetoclax should be administered at the same time or as close together in time as possible.

- Dose modification for adverse events are specified in Section 5.4.2.5

5.3.2. Randomization Phase

Subjects will be randomized in a 1:1 ratio based on their MRD status (see below) after at least 12 cycles of ibrutinib + venetoclax combination therapy. Subjects will be stratified by IGHV status in each randomization strata.



5.3.2.1. Randomization Phase – MRD-negative Subjects (Double-blind)

In the Randomization Phase, subjects who are MRD-negative will be randomized in a blinded fashion to ibrutinib or placebo.

Ibrutinib

- Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression (post reintroduction when applicable) or unacceptable toxicity

OR

Placebo

- Orally once daily matching placebo capsules (3 capsules) continuously until confirmed MRD-positive relapse, disease progression or unacceptable toxicity

5.3.2.2. Randomization Phase – MRD-Positive Subjects (Open-Label)

In the Randomization Phase, subjects who do not achieve confirmed MRD-negative response (MRD-positive) will be randomized to receive open label treatment of I+V vs ibrutinib alone (venetoclax discontinued). For subjects receiving I+V, venetoclax can be administered for up to approximately 2 years per treatment course, until PD or unacceptable toxicity, or until this arm's study closure, whichever is earlier. Subjects continuing on ibrutinib at time of study arm closure

may be offered a separate extension study to continue ibrutinib. The randomization will be stratified by IGHV status.

Ibrutinib + Venetoclax

- Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression or unacceptable toxicity

plus

- Orally once daily venetoclax 400 mg (four 100 mg tablets)

OR

Ibrutinib

- Orally once daily ibrutinib 420 mg (3 capsules) continuously until disease progression or unacceptable toxicity

Reintroduction of Ibrutinib or Venetoclax (MRD Cohort)

Upon confirmed MRD-positive relapse in MRD-negative randomized subjects or confirmed disease progression by IWCLL criteria in any randomized subjects, ibrutinib and/or venetoclax may be reintroduced (Figure 2).

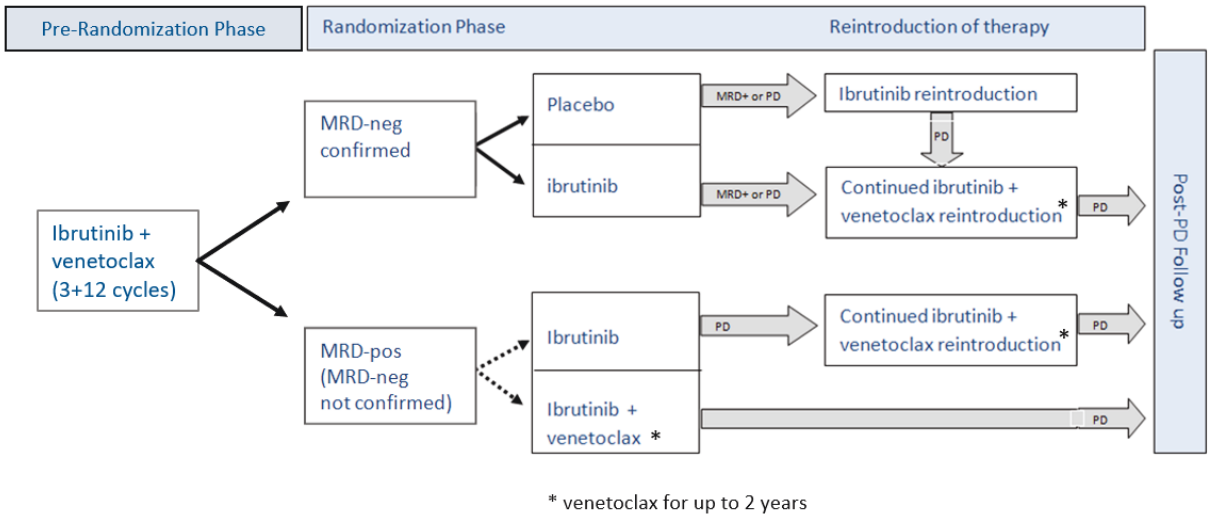
Subjects who are receiving placebo treatment, when MRD-positive relapse or disease progression are confirmed, may reintroduce oral daily ibrutinib until disease progression or unacceptable toxicity.

Subjects who are receiving oral daily ibrutinib, when MRD-positive relapse or disease progression are confirmed, may reintroduce oral daily venetoclax. Standard TLS risk assessment, venetoclax dose ramp up, and TLS management should be employed at venetoclax reintroduction.

For those subjects who were treated with reduced dose(s) of ibrutinib or venetoclax during the Pre-randomization or Randomization Treatment Phase, a dose adjustment at the initiation of the Reintroduction period may be required, with escalation to full dose as tolerated.

The primary analysis for the MRD cohort will be performed at the point that all randomized subjects have had the opportunity to complete at least 12 cycles of randomized treatment or follow-up, and at that time the Sponsor may elect to discontinue follow-up of specific MRD cohort treatment arms on PCYC-1142-CA. For subjects receiving I+V, venetoclax can be administered for up to approximately 2 years per treatment course, until PD or unacceptable toxicity, or until these arm's study closure, whichever is earlier. Subjects who are continuing on ibrutinib at the time of study arm closure may be offered a separate extension study to continue ibrutinib.

Figure 2. Reintroduction of Ibrutinib or Venetoclax for MRD Cohort



5.3.3. Fixed Duration Cohort

- Eligible subjects will receive single-agent ibrutinib (420 mg/day PO) as lead-in treatment for 3 cycles. Starting at Cycle 4, venetoclax will be initiated (with the standard dose ramp up to the target dose of 400 mg/d) utilizing the dose ramp-up schedule in Section 5.4.2.3 Figure 1 and added to the ibrutinib (420 mg/day PO) regimen. The combination will be administered continuously for 12 cycles, until completion of Cycle 15 unless discontinued early for toxicity.

- Venetoclax and ibrutinib should be dosed together at the same time each day with a meal and water
  - For subjects not able to swallow all ibrutinib capsules and venetoclax pills at the same time, administration should be completed within a 60-minute window.

Dose modification for adverse events are specified in Section 5.4.2.5.

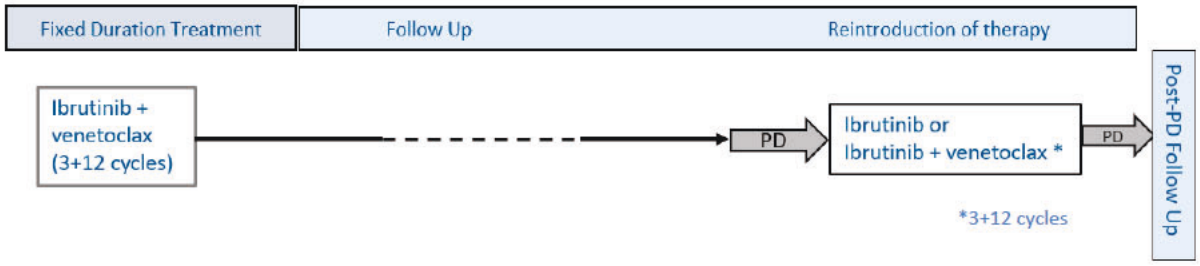
NOTE: If dictated by emerging data from this study, the duration of combined ibrutinib + venetoclax treatment may be modified to ensure appropriate risk-benefit is maintained, compared to historical controls and other emerging data.

Reintroduction of Ibrutinib or Ibrutinib + Venetoclax (FD Cohort):

Subjects with confirmed progression per IWCLL criteria after completion of the fixed duration regimen can be retreated with continuous single agent ibrutinib until disease progression or unacceptable toxicity because it is an established standard of care for treatment of relapsed CLL. For subjects that experience durable efficacy after I+V (ie time to progression after fixed duration regimen is completed of >2 years), retreatment with the I+V fixed duration treatment regimen may be considered based on Investigator's clinical discretion and Medical Monitor's approval. Retreatment is for 15 cycles, PD or unacceptable toxicity, whichever is earlier (Figure 3).

For those subjects who were treated with reduced dose(s) of ibrutinib or venetoclax during the fixed duration treatment phase, a dose adjustment at the initiation of the Reintroduction period may be required, with escalation to full doses as tolerated.

Figure 3 Reintroduction of Ibrutinib or I+V Therapy for FD Cohort



5.3.4. Baseline TLS Assessment

All subjects will be assessed for TLS risk at baseline and prior to commencement of venetoclax dosing using the previously described approach based on tumor burden (Seymour 2014), and consistent with the VENCLEXTA® (venetoclax) prescribing information and noted in Section 5.4.2.2. See Section 7.1.1.9 and Section 7.1.1.10 for TLS risk assessment and prophylaxis respectively.

Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.

5.4. Study Medication

5.4.1. Ibrutinib

5.4.1.1. 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.

5.4.1.2. 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. During cycles with venetoclax combination dosing, ibrutinib and venetoclax should be taken together at the same time, with 8 ounces of water and with a meal (or within 30 minutes after the completion of a meal). For subjects not able to swallow all ibrutinib capsules and venetoclax tablets at the same time, administration should be completed within a 60-minute window. The use of strong CYP3A inhibitors/inducers, and grapefruit, Seville oranges, and starfruit should be avoided for the duration of the study (Appendix G).

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. On days of PK sample collection (C2D1 and C6D1), ibrutinib and venetoclax should be administered at the same time or as close together in time as possible in the clinic. 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 redispensed to anyone.

5.4.1.3. 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 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 subjects. 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.

5.4.1.4. Dose Modification for Adverse Reactions

The dose of study drug must be modified according to the dose modification guidance in Table 2 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 nausea, or Grade 3 or 4 vomiting or diarrhea, if persistent despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. *If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).*

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

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib 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. Dose changes must be recorded in the Dose Administration eCRF. Study treatment should be discontinued in the event of an ibrutinib-related toxicity requiring dose hold lasting more than 28 days, unless reviewed and acknowledged by the Medical Monitor.

Note: Temporary withholding of single-agent ibrutinib 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.

Table 2. 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

For required dose modification for hepatic impairment refer to Section 5.4.1.6 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.1.

5.4.1.5. 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.

5.4.1.6. 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 K).

5.4.2. Venetoclax (ABT-199)

5.4.2.1. Formulation/Packaging/Storage

Venetoclax tablets are provided as film coated tablets containing 10 mg, 50 mg, or 100 mg of venetoclax.

The venetoclax tablets will be packaged in blister packs during initial dose ramp up period and in high density polyethylene (HDPE) plastic bottles thereafter to accommodate the study design. Each container will be labeled as required per country requirements. Labels must remain affixed to the container.

The venetoclax supplied in this study is for investigational use only, and must only be used within this study. All study drug must be maintained under adequate security and stored under conditions specified on the label until dispensed for subject use or returned to Pharmacyclics or representative.

The tablets must be stored at a controlled room temperature of 15° to 25°C (59° to 77°F).

5.4.2.2. Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Subjects with high tumor burden are a greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Subjects at high risk of TLS (at least one lesion ≥10 cm; or at least one lesion ≥5 cm plus circulating lymphocytes >25,000 cells/μL) will be hospitalized during the first 24-48 hours of treatment for TLS monitoring and hydration. Hospitalization should be considered for subjects with medium risk of TLS and baseline creatinine clearance <80 mL/min. Hospitalization for subjects lacking immediate access to a facility capable of correcting TLS promptly or for subjects who are otherwise considered at risk for TLS is allowed at the discretion of the investigator.

In all subjects, perform tumor burden assessments, including radiographic evaluation (eg, CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax in Cycle 4.

In all subjects, assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to subjects prior to first dose of venetoclax to reduce risk of TLS. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk increases.

Table 3. TLS Prophylaxis Based on Tumor Burden from Clinical Trial Data (consider all co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm	Oral (1.5-2 L) and consider	Allopurinol[b]	Outpatient

	OR ALC ≥25 x10^9/L	additional intravenous		• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for subjects with CrCl <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol[b]; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8, and 24 hours

ALC = absolute lymphocyte count; LN = lymph node.

a. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

c. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

d. For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose. A ±30-minute window is acceptable for the 4 and 8 hr chemistry assessments, a ±1 hr window is acceptable for the 12-hour chemistry assessments, and a ±2-hour window is acceptable for the 24-hour chemistry assessments.

e. Hematology and Serum Chemistry may be collected up to 24 hours prior to each venetoclax ramp-up (Cycle 4 Weeks 2-4 and Cycle 5 Week 1), to allow for flexibility in start of ramp-up dose. Hematology and serum chemistry can be drawn on day of dosing to allow for comparisons, but results are not required before dosing decision is made

Hydration: Ensure adequate hydration prior to initiating therapy with venetoclax and throughout the ramp-up phase, especially the first day of each ramp-up dose. Administer intravenous (IV) fluids as indicated based on overall risk of TLS or for those who cannot maintain adequate oral hydration.

Anti-hyperuricemic agents: Administer uric acid reducing agents (eg, allopurinol).
Start 2-3 days prior to initiation of venetoclax; consider continuing through the ramp-up phase.

Laboratory Assessments:

Pre-dose: Assess blood chemistries (specifically creatinine, uric acid, potassium, phosphorus, and calcium) prior to initiating venetoclax to evaluate kidney function and correct pre-existing

hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia to normal levels before administering venetoclax. Reassess blood chemistries before starting each subsequent ramp-up dose of venetoclax.

Post-dose: For subjects at low or medium risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours after initiating venetoclax at the 20 mg and 50 mg doses. For subjects at high risk of TLS, monitor blood chemistries in the hospital at 4, 8, 12 and 24 hours after initiating venetoclax at the 20 mg and 50 mg doses; subsequent ramp-up doses can be administered in the outpatient setting with monitoring of blood chemistries at 6-8 hours and at 24 hours after initiating venetoclax. Electrolyte abnormalities should be corrected promptly. The next dose of venetoclax should not be administered until the 24-hour blood chemistry results have been evaluated and hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia are corrected to normal levels.

Hospitalization: Based on investigator assessment of TLS risk, subjects at high risk of TLS require hospitalization on the day of the first dose of venetoclax 20 mg and 50 mg doses for more intensive prophylaxis and monitoring through the first 24 hours. Subsequent ramp-up doses can be administered on an outpatient basis; however, hospitalization may be considered based on reassessment of risk. See Appendix H for TLS Risk Categories and Appendix J for Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis.

5.4.2.3. Dose and Administration

Venetoclax tablets are taken orally once daily with a meal and water. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. During cycles with ibrutinib combination dosing, ibrutinib and venetoclax should be taken together at the same time, with 8 ounces of water and with a meal (or within 30 minutes after the completion of a meal). For subjects not able to swallow all ibrutinib capsules and venetoclax tablets at the same time, administration should be completed within a 60-minute window. If the subject misses a dose of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible on the same day and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and resume the usual dosing schedule the following day.

In cases of vomiting after taking venetoclax, no additional dose (tablets) should be taken that day. The next dose should be taken at the usual time the following day.

The first dose of venetoclax will be delivered in the clinic (or in the hospital depending on TLS risk category) on Cycle 4 Day 1. Seven doses of daily venetoclax must be taken at each dose level in the venetoclax dose ramp up, thus each level of the ramp up may require more than 7 days if doses are missed or held. After completion of the 5-week dose ramp up, subsequent dosing is typically on an outpatient basis. On days of PK sample collection (C2D1 and C6D1), ibrutinib and venetoclax should be administered at the same time or as close together in time as

possible in the clinic. Venetoclax will be dispensed to subjects in blister packs through the dose ramp up period, and in bottles at each subsequent visit. Unused venetoclax dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned tablets must not be redispensed to anyone.

Assess subject-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to subjects prior to first dose of venetoclax to reduce risk of TLS. Venetoclax will be administered orally once daily (QD) beginning with a dose ramp-up period. As shown in Figure 1, the initial venetoclax dose is 20 mg QD. After one week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after one week, to 100 mg QD, 200 mg QD and the maximum dose of 400 mg QD. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS. All study subjects will be categorized in Cycle 3 according to their risk for developing TLS. Their dose management including during the dose ramp-up period will be conducted in accordance with their risk for developing TLS (see Section 5.4.2.5) and may include dose delay and/or dose reduction as required for prophylaxis and management of TLS.

5.4.2.4. Overdose

There is no specific antidote for venetoclax. For subjects who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt venetoclax and monitor carefully for signs and symptoms of TLS along with other toxicities (see Section 1.3.3 and Section 5.4.2). Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

5.4.2.5. Dose Modification for Adverse Reactions

Dosing interruption and/or dose reduction may be required. See Table 4 for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the dose ramp-up schedule).

Table 4. Venetoclax Recommended Dose Modifications for Toxicities[a]

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS (see Howard Criteria in Appendix I)	Any	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5)
		For any events of clinical TLS[b], resume at a reduced dose following resolution (see Table 5).

Event	Occurrence	Action
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
ANC <1000/µL with infection or fever; or CTCAE Grade 4 hematologic toxicities (ANC <500/µL, WBC <1000/µL, platelets <25,000/µL, life threatening anemia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to ANC >1500/µL or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.

Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.

a. Adverse reactions were graded using NCI CTCAE version 4.03.

b. Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

Table 5. Dose Modification for Toxicity during Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

a. During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

For required dose modification for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.2.

5.4.2.6. Management of Neutropenia

Nonclinical and clinical experience indicates that venetoclax may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk.

CTCAE Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for subjects with severe neutropenia. Supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors (eg, G-CSF) should be considered.

5.4.2.7. Management of Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Venetoclax treatment should be withheld for any CTCAE Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

5.4.2.8. Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant CTCAE Grade ≥3 non-hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

5.4.2.9. Management of Decrease in Spermatogenesis

Venetoclax may cause a decrease in spermatogenesis. Male subjects considering preservation of fertility should bank sperm before initiating treatment with venetoclax.

5.4.2.10. Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using venetoclax. Advise females of reproductive potential to avoid pregnancy during treatment. If venetoclax is used during pregnancy or if the subject becomes pregnant while taking venetoclax, the subject should be apprised of the potential hazard to the fetus.

5.4.2.11. Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following venetoclax therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and thereafter until B-cell recovery.

5.5. Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject discontinues one study drug for reasons other than disease progression, the other study drug should be continued per protocol. Refer to Study Design details in Section 3.1.1 and Section 3.1.2. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

An End-of-Treatment Visit (Section 8.7) is required for all subjects except for those subjects who have withdrawn full consent.

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 and patient should receive full supportive care during study participation (including fluids and electrolyte replacement, and antibiotics when appropriate). 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 6.2 below. Transfusions may be given in accordance with institutional policy.

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.

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

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

6.2. Medications to Be Used with Caution

A sample list of cautionary medications with ibrutinib and venetoclax is provided in Appendix G. Refer to

Table 6 below for management of potential ibrutinib and venetoclax interactions with CYP3A inhibitors.

6.2.1. Drugs That May Alter Ibrutinib and/or Venetoclax Plasma Concentrations

6.2.1.1. Concomitant Use with Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.4.1.2).

- If a strong CYP3A inhibitor must be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib for the duration of inhibitor use.
- If a strong CYP3A inhibitor must be used, the benefit outweighs the risk, and longer term dosing is required (for more than 7 days), reduce ibrutinib dose to 140 mg for the duration of inhibitor use.
    - If posaconazole at higher doses (suspension >200 mg twice daily), or IV or delayed-release formulations must be used, reduce ibrutinib dose to 140 mg for the duration of azole use
- If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 280 mg for the duration of the inhibitor use.
    - If voriconazole, or doses ≤200 mg twice daily of posaconazole suspension are required, reduce ibrutinib dose to 140 mg for the duration of inhibitor use.
- No dose adjustment is required in combination with mild inhibitors.
- Subjects should be monitored closely for signs of ibrutinib toxicity
- After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort) as these medications/products could decrease ibrutinib concentrations. Consider alternative agents with less CYP3A induction.

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp).

A list of common CYP3A inhibitors and inducers is provided in Appendix G. For further information, please refer to the current version of the ibrutinib IB.

6.2.1.2. Concomitant Use with Venetoclax

- Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase increases the risk for TLS. Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.

- For subjects who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used concomitantly with a strong CYP3A inhibitor. See Section 6.3.1 for prohibited CYP3A inhibitors.

- Avoid concomitant use of moderate CYP3A inhibitors with venetoclax. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the doses of venetoclax by at least 50%. Monitor subjects more closely for signs of toxicities.

- Avoid concomitant use of strong CYP3A inhibitors with venetoclax. Consider alternative treatments. If a strong CYP3A inhibitor must be used, reduce the doses of venetoclax by at least 75%. Monitor subjects more closely for signs of toxicities.

Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

A list of common CYP3A inhibitors, CYP3A inducers, and cautionary medications is provided in Appendix G.

For preliminary venetoclax PK results with concurrent ibrutinib administration, see Section 1.3.2.1. For further information, please refer to the current version of the venetoclax IB.

Table 6. Management of Potential Ibrutinib and Venetoclax Interactions with CYP3A Inhibitors

Inhibitors	Venetoclax		Ibrutinib
	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)	At any time
Strong CYP3A Inhibitor	Contraindicated	Avoid inhibitor use, consider alternate. If must be used, reduce the venetoclax dose by at least 75%	Avoid inhibitor use, consider alternative agent. If must be used, withhold ibrutinib for duration of inhibitor use, or reduce ibrutinib to 140 mg
Moderate CYP3A Inhibitor	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 50%		Avoid inhibitor use, consider alternative agent. If must be used, reduce ibrutinib to 280 mg

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. Drugs That May Have Their Plasma Concentrations Altered by Venetoclax

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*. To avoid a potential interaction in the gastrointestinal tract, co-administration of narrow therapeutic index P-gp substrates such as digoxin with venetoclax should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

6.2.4. 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. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. 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. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries 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 be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in subjects receiving warfarin.

6.3. Prohibited Concomitant Medications and Products

6.3.1. Prohibited Concomitant Medications and Products for Ibrutinib and/or Venetoclax

Any non-study protocol related chemotherapy, anti-cancer immunotherapy, experimental therapy, or radiotherapy for the underlying B-cell malignancy are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying malignancy are prohibited (Refer to Section 6.1 for further guidance).

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

Use of strong CYP3A inhibitors is contraindicated during venetoclax initiation and dose ramp-up. Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

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 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). 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 first dose on Day 1 (Section 4).

7.1.1.3. Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. The medical history collection period is defined as disease history up until first dose. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis, Rai staging (Appendix M) within 28 days of first dose with study drug will be recorded.

7.1.1.4. Prior and Concomitant Medications

All active medications from the signing of ICF or at least 14 days prior to first dose through 30 days after the last dose of study drug will be documented.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event (AE) is provided in Section 11.1. The occurrence of AE from the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug until 30 days after the last dose of study drug that meet the AE definition must be recorded as

AEs in the eCRF. Laboratory abnormalities designated clinically significant by the investigator will also be documented as AEs. Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6. Physical Examination

The Screening and End-of-Treatment 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.

7.1.1.7. ECOG

The ECOG performance status is provided in Appendix F. Performance status will only be collected until disease progression.

7.1.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, and body temperature after the subject has rested in a sitting position for at least 3 minutes.

7.1.1.9. Tumor Lysis Syndrome (TLS) Risk Assessment

At baseline and prior to initiating venetoclax in Cycle 4, all study subjects will be assessed for risk of developing TLS. Ongoing risk of TLS should be assessed at all ramp up visits. The risk of TLS is a continuum based on multiple factors, including comorbidities. Subjects with high tumor burden (eg, any lymph node with a diameter ≥5 cm or high absolute lymphocyte count (ALC) [ALC ≥25 x 10^9/L]) are at greater risk of TLS when initiating venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Tumor burden assessments, including radiographic evaluation (eg, CT scans) as well as blood chemistry (creatinine, uric acid, potassium, phosphorus, and calcium) assessments will be performed in all subjects prior to initiating venetoclax treatment.

Appropriate venetoclax dosing and management of subjects throughout their study treatment is guided by their individual risk for developing TLS. Risk-based TLS prophylaxis and management measures are described in Section 5.4.2.2.

7.1.1.10. Tumor Lysis Syndrome (TLS) Prophylaxis

For subjects at risk of TLS per investigator assessment, the prophylaxis measures listed in Section 5.4.2.2 should be followed and more intensive measures (including hospitalization) should be employed as overall risk increases. These measures should be performed prior to initiating therapy with venetoclax (2-3 days prior to first dose) and throughout the ramp-up

phase, especially the first day of each ramp-up dose. Refer to Schedule of Assessments (Appendix A, Appendix B, Appendix D, and Appendix E) for specific timepoints of assessments.

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, bands, lymphocytes, prolymphocytes, atypical lymphocytes (if found on routine CBC review), monocytes, eosinophils, basophils. Hematology samples will be collected and tested by local laboratory.

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/Urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate/inorganic phosphorus, uric acid, magnesium, bicarbonate. Chemistry samples will be collected and tested by local laboratory.

7.1.2.3. Coagulation Studies

Measurement of PT/INR and aPTT will be performed at Screening and Reintroduction using a local laboratory.

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis B surface antigen (HBsAg). If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to enrollment. Subjects who are HBsAg positive are excluded. Hepatitis serologies will be collected and tested by local laboratory.

7.1.2.5. Serum β2-microglobulin

One blood sample for β2-microglobulin will be collected and tested by local laboratory at C1D1 and Cycle 10 for subjects in the FD Cohort (see Appendix B).

7.1.2.6. Pregnancy Test

Serum pregnancy test will be required at Screening by local laboratory only for women of childbearing 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

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

During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

At Screening, and if clinically indicated during the conduct of the study, 12-lead ECG will be done *in triplicate* (≥1 minute apart) in supine position after resting at least 10 minutes.

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

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.

De-identified copies of all imaging will be submitted to the Sponsor or designee.

7.1.3.3. Bone Marrow Biopsies and Aspirate

Bone marrow biopsy and aspirate samples will be assessed locally and used for disease assessment by Investigator, to confirm complete response, to confirm cytopenic progression attributable to CLL, and distinguish autoimmune and treatment-related cytopenias. Bone marrow components should be evaluated for complete response per 2008 IWCLL criteria including relative cellularity for patient's age, % lymphocytes, and for the presence of B lymphoid nodules.

In the MRD cohort: Bone marrow aspirate will be used for MRD assessment by central lab flow cytometry at C16D1 and visits with CR assessments. A Cycle 29 bone marrow aspirate should be obtained to confirm ongoing MRD-negativity or attainment of new MRD-negativity (see below for additional details).

In the Fixed Duration cohort: Bone marrow aspirate will be used for MRD assessment by central lab flow cytometry at the following: C10D1, visits with CR assessments, and the C19D1 assessment (3-months after the completion of Cycle 15) (see below for additional details).

Table 7 Overall Response Assessment

	BM Biopsy	BM Aspirate	Peripheral Blood
Clinical response (or progression when appropriate)	X (and at select cycles – see Table 8 and Table 9)	X (any time a BM biopsy is collected to confirm CR, also collect an aspirate for MRD)	X
MRD		X (at select cycles, see Table 10 and Table 11)	X (at select cycles, see Table 10 and Table 11)

Table 8. MRD cohort: Bone Marrow Biopsy and Aspirate Collection Times for Clinical Response

	Screening Visit	C16D1 Visit (± 14 days)	C29D1 Visit (± 14 days)	Suspected CR Visit	Suspected PD Visit
BM Biopsy (local lab and central lab)	X[b]	X[a,c,f]	X[a,f]	X[a,f]	X[e]
BM Aspirate (local and central lab)	X[b]	X[a,c,f]	X[a,d,f]	X[a,f]	X[e]

a. BM biopsy and aspirate for clinical response assessment (local lab and [redacted] central lab); BM aspirate used for MRD assessment, and [redacted] studies (MRD central lab)
b. Unless previously collected within 90 days prior and not needed for karyotype, a portion of BM biopsy and aspirate is forwarded to the central laboratory for assessment
c. Unless collected prior and within 3 months for CR assessment, and confirmed CR and MRD-negative in BM
d. Collected in randomized subjects, and in any subject w/ MRD-neg conversion in PB
e. Only required to document PD by cytopenic progression, as appropriate (local lab)
f. If the bone marrow biopsy and aspirate results demonstrate a hypocellular marrow, a repeat biopsy (in 4 weeks up to 6 months) is needed per IWCLL Guidelines (see Section 7.2.3.2)

Table 9. Fixed Duration cohort: Bone Marrow Biopsy and Aspirate Collection Times for Clinical Response

	Screening Visit	C10 (±14 days)	C19 (3 mo after completion of C15 combo [±14 days])	Suspected CR Visit	Suspected PD Visit
BM Biopsy (local and central lab)	X (local only)	X[a,c,d]	X[a,d]	X[a,d]	X[b]
BM Aspirate (local and central lab)		X[a,c,d]	X[a,d]	X[a,d]	X[b]

a. BM biopsy and aspirate for clinical response assessment (local lab and [redacted] central lab); BM aspirate used for MRD assessment, and [redacted] studies (MRD central lab)
b. Only required to document PD by cytopenic progression, as appropriate (local lab)
c. Unless collected prior and within 3 months for CR assessment, and confirmed CR and MRD-negative in BM
d. If the bone marrow biopsy and aspirate results demonstrate a hypocellular marrow, a repeat biopsy (in 4 weeks up to 6 months) is needed per IWCLL Guidelines (see Section 7.2.3.2)

At Screening (MRD and FD Cohorts)

A unilateral bone marrow biopsy must be obtained at Screening or up to 90 days before enrollment for disease confirmation.

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); NOTE: The bone marrow trephine will be split in half with one portion to remain at the site for local assessment and the other half sent to the central laboratory
- Bone marrow aspirate

If insufficient marrow biopsy material or slides are available to be submitted, high resolution images of the available representative slides should be acquired and submitted instead.

Copies of redacted bone marrow pathology reports for samples reviewed locally will be collected and may be reviewed by the Sponsor and/or IRC.

For Response Evaluation (MRD and FD Cohorts)

At every Overall Response Assessment with a scheduled BM evaluation (Table 9 for MRD cohort and Table 10 for FD cohort), or if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters at other time points (Suspected CR), a bone marrow aspirate and biopsy must be obtained to confirm the CR and to evaluate minimal residual disease.

Bone marrow collected to confirm CR must have minimal residual disease (MRD) assessed by flow cytometry on the aspirate (see below for more details). In cases where cytopenic progression is suspected, the bone marrow aspirate or biopsy should be used to distinguish autoimmune and drug-related cytopenias.

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) NOTE: The bone marrow trephine will be split in half with one portion to remain at the site for local assessment and the other half sent to the central laboratory
    - Bone marrow aspirate

If insufficient marrow biopsy material or slides are available to be submitted, high resolution images of the available representative slides should be acquired and submitted instead.

Copies of redacted local bone marrow pathology reports for samples reviewed locally will be collected and may be reviewed by the Sponsor and/or IRC.

Quantitative Minimal Residual Disease (MRD) Assessment by Central lab

A C1D1 PB sample will be submitted for MRD evaluation to establish a baseline immunophenotypic profile. Starting from C7D1 on, MRD will be assessed by PB every 3-12 cycles. Refer to Table 10 and Table 11for MRD sample collection schedule.

In the MRD Cohort:

A bone marrow aspirate will be collected from all subjects for assessment of MRD status at Cycle 16 (±14 days) unless collected previously in those with a documented CR and MRD-neg confirmed in BM after the start of study treatment. An additional bone marrow aspirate should be collected at Cycle 29 (±14 days) in randomized subjects, and in any subject with MRD-neg conversion in PB.

In subjects who consent, an additional bone marrow aspirate (after suspected CR or C16) can be collected prior to randomization to serially confirm MRD-negativity in the BM compartment.

Table 10. MRD Cohort: MRD Sample Collection Schedule

	C1 D1	C7 D1	C10 D1	C13 D1	C16D1 (±14 days)	C20-C29D1 Q3 cycles (±14 days)	C35D1 and Q6 cycles thereafter	To Confirm CR	To Confirm MRD+ Relapse	End of Treatment
BM Aspirate					X[a]	X (C29)[a,b,c]		X		
Peripheral Blood	X	X	X	X	X	X	X	X	X	X

a. Unless collected prior for CR assessment, and were MRD-neg in BM
b. Collected in randomized subjects, and in any subject w/ MRD-neg conversion in PB
c. ±14 day window applies to BM aspirate only

In the Fixed Duration Cohort:

A bone marrow aspirate will be collected from all subjects for assessment of MRD status at Cycle 10 and 3 months after the completion of Cycle 15 (ie, C19). Bone marrow assessments can be performed if needed to confirm CR.

Table 11. Fixed Duration Cohort: MRD Sample Collection Schedule

	C1D1	C7D1 (±14 days)[a]	C10D1 (±14 days)[a]	C13D1 (±14 days)[a]	EOT (within 30 days of last study drug; C17 for those who complete regimen)	C19D1, C25D1, C28D1, C31D1 and annually thereafter (±14 days)[a]
BM Aspirate		[X - if needed to confirm CR]	X	[X - if needed to confirm CR]		X C19D1
Peripheral Blood	X	X	X	X	X	X
			Every 3-12 cycles [a]			

a. ±14 day window applies to BM aspirate only

7.1.3.4. FISH Assays

Cytogenetic profiles will use CLL FISH probes to detect abnormalities in chromosomes 11q, 12, 13q, and 17p.

For all subjects, peripheral blood for FISH will be collected at C1D1 and at Day 1 of reintroduction of study drug.

7.1.3.5. Karyotype

Karyotype will be derived from PB (or BM aspirate- MRD Cohort only) using a stimulated culture method. BM aspirate will be used in lieu of PB when the ALC is ≤4000 in MRD cohort.

If a BM was collected within 90 days prior to screening and the ALC is ≤4000 then another BM aspirate will be required before C1D1 first dose and at Day 1 of reintroduction of study drug.

7.1.4. Pharmacokinetics/[redacted]

7.1.4.1. Pharmacokinetics – MRD Cohort Only

Pharmacokinetics of ibrutinib and its metabolite PCI-45227 will be determined at steady-state during the Pre-randomization Phase, single-agent ibrutinib (lead-in period) on Day 1 of Cycle 2 at time-points specified in Table 12 below in the MRD cohort only. Pharmacokinetics will not be assessed in the Fixed Duration cohort. Ibrutinib and venetoclax should be dosed together at the same time with 8 ounces of water and a meal. For subjects not able to swallow all ibrutinib capsules and venetoclax pills at the same time, administration should be completed as close together in time as possible. It is anticipated that steady state will be reached after 1 week of administration of the highest venetoclax dose (400 mg). Pharmacokinetic samples (PK) should only be collected when treatment has been without interruption for at least 7 days. In the case of treatment interruption, pharmacokinetic sampling should be delayed until completion of an uninterrupted 7 days of dosing. In cases of dose reduction, pharmacokinetic sampling should be delayed until completion of an uninterrupted 7 days of consistent dosing.

Pharmacokinetics of ibrutinib and venetoclax when dosed in combination will be also determined at steady-state on Day 1 of Cycle 6 at time-points specified in Table 12 below.

Table 12. Pharmacokinetic Sample Schedule for Ibrutinib and Venetoclax (MRD Cohort Only)

Study Drug PK	Cycle[f]	Day	Pre-dose PK[c] & Meal[d]	Study Drug Dose[e]	Time after ibrutinib or ibrutinib + venetoclax				
					1 hour (± 15 min)	2 hour (± 15 min)	4 hour (± 30 min)	6 hour (± 30 min)	8 hour (± 1 h)
Ibrutinib	2[a]	1	X	X	X	X	X	X	X
Ibrutinib & Venetoclax	6[b]	1	X	X	X	X	X	X	X

a. Ibrutinib single-agent only steady-state PK
b. Ibrutinib and venetoclax combination steady-state PK
c. Predose samples should be collected 30 minutes prior to the administration of ibrutinib (lead-in period) or ibrutinib and venetoclax (combination period)
d. The meal to be completed within 30 minutes
e. Ibrutinib/venetoclax to be dosed 30 minutes after the start of the meal
f. PK should only be drawn when ibrutinib (C2), and ibrutinib with venetoclax (C6) are at steady state plasma levels. If any dose of ibrutinib and/or venetoclax were withheld in the week prior to C2D1, and C6D1, then

PK assessment should be rescheduled to the next study visit day after doses have been consistently administered for ≥1 week

Example:

Predose PK --7:00a
Breakfast ----7:00a to 7:30a
Dose ----------7:30a
1 hr PK ------8:30a
2 hr PK ------9:30a
4 hr PK ------11:30a
6 hr PK ------1:30p
8 hr PK ------3:30p

Refer to the laboratory binder 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 is needed during the PK collection period, administration of concomitant medications should be recorded.

Pharmacokinetics Sample Collection for Subjects Treated with a Concomitant CYP3A Inhibitor While on Ibrutinib and/or Venetoclax Treatment

For subjects who must start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib and/or venetoclax, additional PK blood samples for evaluation of ibrutinib and/or venetoclax exposure are requested approximately one week post-initiation of concomitant CYP3A inhibitor. PK samples will be collected at:

- Pre-dose (If possible, sample should be obtained 22-24 hours post the previous day's dose and before dosing on the day of the scheduled visit)
- 1 hour ± 15 min
- 2 hours ± 15 min
- 4 hours ± 30 min
- 6 hours ± 30 min
- 8 hours ± 1 h

7.1.4.2. [redacted]

[redacted]

[redacted]

7.1.4.3. [redacted]

[redacted]

7.1.4.4. [redacted]

[redacted]

7.2. Efficacy Evaluations

Clinical 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 local laboratory
- Radiographic evaluation (CT or MRI scan of the neck, chest, abdomen, and pelvis)
- Bone marrow biopsy (as appropriate) if there is evidence of CR in the other response parameters.

If study drug is held before a scheduled clinical 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.

Clinical efficacy assessments, for the purpose of the study result analyses, will be performed by Investigators. For response assessments not requiring a CT scan, the Investigator should evaluate response based on available clinical data, including physical examination and laboratory results. For the MRD and Fixed Duration cohorts, imaging will be collected and stored centrally. The Sponsor may utilize IRC for independent review of efficacy with details to be outlined in the separate IRC charter.

MRD Evaluations:

Samples for MRD analysis will be sent to a central laboratory that has a validated flow cytometry assay that has a limit of detection of 10^{-4}. MRD will be assessed in the following compartments:

- Bone marrow
- Peripheral blood

7.2.1. Definitions

7.2.1.1. 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. A 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 the Investigator.

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.

7.2.1.2. 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 (hemoglobin 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 2016 guidelines, supporting that subjects with isolated lymphocytosis in the setting of improvement in other disease parameters should not be considered to have clinical progressive disease or treatment failure (Cheson 2012).

7.2.1.3. 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.

7.2.1.4. Minimal Residual Disease (MRD)

MRD is a low-level of disease that persists, and which is not detectable with routine imaging nor routine laboratory tests, but can be demonstrated in PB or BM with more sensitive flow cytometry assays.

7.2.1.4.1. MRD-Negativity

MRD-negativity is defined as <1 CLL cell per 10,000 leukocytes ($<1 \times 10^{-4}$), as assessed by flow cytometry of a peripheral blood (PB) or bone marrow (BM) aspirate sample.

Confirmed MRD-negative response for randomization purposes requires MRD-negativity serially over at least 3 cycles, with negativity in both BM and PB. Subjects who do not achieve confirmed MRD-negative status are not considered to have a MRD-negative response for randomization purposes in the MRD cohort. See Section 7.1.3.3 for MRD assessment schedule.

7.2.1.4.2. MRD-Positive Relapse (MRD Cohort Only)

MRD-positive relapse is defined as an increase in CLL cells ≥1 per 100 leukocytes ($\geq 1 \times 10^{-2}$) confirmed on two separate serial occasions, after a confirmed MRD-negative response, as assessed by flow cytometry of a PB or BM aspirate sample.

7.2.2. Guidelines for Clinical Disease Evaluation

Objective response will be categorized as CR, CR with incomplete bone marrow recovery (CRi), nodular partial response (nPR), partial response (PR), PR with lymphocytosis (PRL), stable disease (SD), or progressive disease (PD)—all based upon IWCLL criteria (Hallek 2008, Hallek 2012, Hallek 2013, Cheson 2012). All responses must be maintained for at least 2 months to be considered confirmed. CRs must be confirmed by bone marrow biopsy/aspirate. Response assessments on treatment arms will occur independent of ongoing therapy. For purposes of this protocol, 2 months equals 2 cycles (56 days) with each cycle equaling 28 days.

Given the known mechanism of action of BCR-inhibiting agents, including ibrutinib, and the treatment-related lymphocytosis frequently observed during treatment with ibrutinib, isolated treatment-related lymphocytosis (in absence of other clinical, CT, or laboratory evidence of disease progression) will not be considered progressive disease. This approach is supported by both the authors of the IWCLL 2008 and 2017 guidelines (Hallek 2012, Cheson 2012) and the NCCN.

The requirement for each parameter at baseline to be evaluable throughout the study is outlined in Table 13.

Table 13. 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
Hemoglobin	≤11.0 g/dL

7.2.3. Clinical Response Categories

Investigator assessment of response should include physical examination, radiographic imaging, and evaluation of blood and marrow (if applicable). For response assessments not requiring a CT scan, the Investigator should evaluate response based on available clinical data, including physical examinations and laboratory results. Definition of response for CR, CRi, nPR, PR, PRL and disease progression will be evaluated by the criteria listed in Table 14. Group A criteria define the tumor load and Group B criteria define the function of the hematopoietic system. Response must be confirmed by CT when available, and must last at least 2 months without transfusional support or growth factor product to be considered a confirmed response.

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 >38ºC for ≥2 weeks, no ongoing unintentional ≥10% body weight loss, no night sweats for >1 month without other evidence of infection, no fatigue interfering with work or usual activities) attributable to CLL.
- Neutrophils >1500/µL, 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 after all other criteria meet the definition of CR. To define a CR, the marrow sample must 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.

Table 14. Criteria for Clinical 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[d] in a patient with cytopenias		
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 7.2.1.2).

[d] Hypocelluar marrow is a CRi when peripheral blood cytopenias not meeting Group B criteria are present. CRi requires at least one abnormal Group B criteria.

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

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

Complete response with an incomplete marrow recovery (CRi) is defined as a CR with an incomplete recovery of the subject's bone marrow, manifested by persistent cytopenias. 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. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or when peripheral blood counts have recovered. However, this time interval should not exceed 6 months.

7.2.3.3. Nodular Partial Response (nPR)

Nodular partial response (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 or aggregates are residual disease and therefore the subject is termed an nPR. Immunohistochemistry may be performed to define whether the nodules or aggregates comprise primarily T cells, B cells other than CLL cells, or CLL cells. If nodules or aggregates are not composed of CLL cells, a CR can be documented provided all other criteria are met.

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 ≤4000/µL

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 >1500/µL or ≥50% improvement over baseline
- Platelets >100,000/µL or ≥50% improvement over baseline
- Hgb >11 g/dL or ≥50% improvement over baseline

* Note: For criterion to be considered in response evaluation, it must have been evaluable at baseline

7.2.3.5. PR with Lymphocytosis (PRL)

Subjects achieve all PR criteria with the exception of lymphocyte criteria.

7.2.3.6. Stable Disease (SD)

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

7.2.3.7. Progressive Disease (PD)

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 baseline ALC count and at least 5 x 10^9/L
- New cytopenia (hemoglobin 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 (eg, by PE or ALC) must be confirmed by a serial exam at least 2 weeks later, and confirmed by imaging.

7.2.4. Hematological Improvement

Hemoglobin and platelet counts will be evaluated.

7.2.5. Radiographic Images Assessment

Radiological efficacy assessments, for the purpose of the study result analyses, will be performed by the Investigator. For the MRD and Fixed Duration cohorts, imaging will be collected and stored centrally. The Sponsor may utilize IRC for independent review of efficacy with details to be outlined in the separate IRC 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.

7.3. Suspected Disease Progression

The schedule of assessments is provided in Appendix A and Appendix B. Any suspected case of disease progression will prompt procedures performed in a Suspected Disease Progression visit (Section 8.5). 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 or a single laboratory parameter, this finding should be confirmed by a subsequent evaluation at least 2 weeks later and confirmed by imaging.

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

7.4. 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, Appendix B, Appendix C, Appendix D, and Appendix E) 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

8.1. Screening Period

Screening procedures will be performed up to 30 days prior to initiation of study drug, 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 enrollment 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

- Obtain vital signs (including blood pressure, heart rate, and body temperature) after the subject has rested in the sitting position for at least 3 minutes
- 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 (record as Medical History on eCRF form)
- Imaging by CT or other modality as described in Section 7.1.3.2 (if not performed within 6 weeks prior to enrollment)
- Obtain a bone marrow aspirate and biopsy (if not performed within 90 days prior to enrollment) (local and central labs [MRD Cohort]; local labs [FD Cohort])
- Obtain blood specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry (including creatinine clearance)
  - Coagulation panel (PT/INR, aPTT)
  - Hepatitis serologies
  - Obtain serum pregnancy test for women of childbearing potential only

8.2. MRD Cohort

For the MRD cohort, the study is divided into a Screening Phase, a Pre-randomization Treatment Phase, a Randomization Phase, and a Post-PD Follow-up Phase. The Schedule of Assessments (Appendix A) summarizes the frequency and timing of efficacy, PK, [redacted] and safety measurements applicable to this study. The timing of all 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.

MRD Cohort: Pre-Randomization Treatment Phase

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

Following completion of the Screening Visit and once eligibility has been confirmed (per inclusion/exclusion criteria), subjects will initiate ibrutinib treatment. Venetoclax will be added to ibrutinib treatment and initiated after completion of 3 cycles of ibrutinib. The venetoclax dose will be ramped up over 5 weeks per standing dosing recommendations (see Section 5.3.1 for ibrutinib and venetoclax dosing).

Subjects who are unable to complete at least 12 cycles of combination therapy will not be eligible for Randomization but will continue to follow the same visit schedule until disease progression. After disease progression subjects will enter the Post-PD Follow up Phase (Section 8.8).

8.2.1. Treatment Visits

8.2.1.1. 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 enroll subject. Dosing should occur within 3 days of confirmation.
- Adverse events
- Physical examination
- Vital signs
- ECOG performance status
- Concomitant medications
- Hematology
- Serum chemistry (including creatinine clearance)
- Tumor Lysis Risk assessment (use Screening CT and C1D1 ALC. see Appendix H for risk assessment categories)
- [redacted] assays
- IGHV (if IGHV sample is not informative for any reason, another peripheral blood sample should be drawn and sent to the central lab at the next appropriate timepoint)
- FISH panel
- Karyotype
- Buccal Swab
- MRD in peripheral blood
- Perform urine pregnancy test for women of childbearing potential only

Dosing and Post First Dose

- In-clinic administration of ibrutinib
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.1.2. Cycles 2 and 3 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of each cycle (except for CT/MRI):

- Adverse events
- Concomitant medications

- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- CT/MRI (to assess response and lymph node sum of the product of the diameters [SPD] for TLS risk assessment, Cycle 3 only – to be obtained as close to the beginning of Cycle 4 as possible, while still allowing for appropriate TLS risk-guided interventions including hospitalization if appropriate)
- Hematology
- Serum chemistry
- [redacted] assays [redacted]
- Pharmacokinetics sample (Cycle 2 only. See Section 7.1.4.1 for Pharmacokinetics Sample Collection Schedule)

Dosing and Post Dose

- In-clinic administration of ibrutinib (Cycle 2 only)
- Collection of post dose pharmacokinetics samples per Section 7.1.4.1 (Cycle 2 only)
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.1.3. Cycle 4 Visits

8.2.1.3.1. Pre-Cycle 4 (Pre-initiation of Venetoclax)

The following procedures will be performed 2-3 days (±3 days) prior to Cycle 4:

- Overall response assessment
- Hematology
- Serum Chemistry
- Tumor Lysis Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk)

The following procedures will be performed 1 day prior to Cycle 4:

- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk)

8.2.1.3.2. Cycle 4 Week 1 Day 1

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycle 4, Week 1:

- Adverse events

- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk, venetoclax administration setting, and frequency of serum chemistry monitoring assessments)
- [redacted] assays

Dosing and Post First Dose of Venetoclax

- In-clinic administration of ibrutinib
- In-clinic administration of venetoclax 20 mg for low and medium risk TLS subjects
- Consider hospitalization for first dose of venetoclax 20 mg in medium risk TLS subjects with a CrCl < 80 mL/min
- In-hospital administration of first dose of venetoclax 20 mg for high risk TLS subjects
- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.2.1.3.3. Cycle 4 Week 1 Day 2

Pre-Dose

- Adverse events
- Hematology
- Serum chemistry
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

8.2.1.3.4. Cycle 4 (Week 2 – Week 4) Visits

The following procedures will be performed on Day 1 (±3 days) of Cycle 4, Weeks 2, 3, and 4 (coincides with venetoclax standard dose ramp-up of 50 mg (W2D1), 100 mg (W3D1), and 200 mg (W4D1):

Pre-Dose

- Adverse events

- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Syndrome Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

Dosing and Post-Dose

- In-clinic administration of venetoclax 50 mg (Week 2), 100 mg (Week 3) and 200 mg (Week 4) for low and medium TLS risk subjects
- Consider hospitalization for first dose of venetoclax 50 mg in medium risk TLS subjects with a CrCl < 80 mL/min
- In-hospital administration of first dose of venetoclax 50 mg dose at week 2 for high risk TLS subjects; in-clinic administration of venetoclax 100 mg (Week 3) and 200 mg (Week 4) for high risk TLS subjects
- Dispense venetoclax for offsite use and provide study drug compliance instructions
-

8.2.1.3.5. Cycle 4 Week 2 Day 2

Pre-Dose

- Adverse events
- Hematology
- Serum chemistry
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

8.2.1.4. Cycle 5 Visits

8.2.1.4.1. Cycle 5 Week 1 and Week 3 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycle 5, Week 1 and Week 3:

- Adverse events
- Concomitant medications

- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Syndrome Risk assessment (see Appendix H for risk assessment categories) (Week 1 Only)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk, venetoclax administration setting, and frequency of serum chemistry monitoring assessments) (Week 1 Only)

Dosing and Post-Dose

- In-clinic administration of venetoclax
- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions (Week 1 only)

8.2.1.5. Cycle 6 – Cycle 9 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycles 6, 7, 8, and 9:

- Adverse events
- Concomitant medication
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Overall response assessment (by PE/CBC Cycle 7 only)
- MRD in peripheral blood (Cycle 7 only)
- [redacted] assays ([redacted])
- Pharmacokinetics sample (Cycle 6 only. See Section 7.1.4.1 for Pharmacokinetics Sample Collection Schedule)

Dosing and Post-Dose

- In-clinic administration of ibrutinib (Cycle 6 only)

- In-clinic administration of venetoclax (Cycle 6 only)
- Collection of post dose pharmacokinetics samples per Section 7.1.4.1 (Cycle 6 only)
- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.2.1.6. Cycle 10 & Cycle 13 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycles 10 and13:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- CT/MRI (Cycle 10 only)
- Overall response assessment
- MRD assessment (in peripheral blood)
- [redacted] assays

Post-Dose

- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.2.1.7. Cycle 16 Day 1 Visit

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycle 16:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry

- CT/MRI
- Overall response assessment
- Bone marrow biopsy (unless collected prior for CR assessment, and confirmed MRD-negative in BM)
- MRD assessment (bone marrow aspirate and peripheral blood). Bone marrow aspirate can be drawn ±14 days from C16D1.
- [redacted] assays

Post-Dose

- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

MRD Cohort: Randomization Phase

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

At Cycle 17 (following 3 cycles of ibrutinib lead-in, completion of 12 cycles of ibrutinib + venetoclax combination treatment, plus 1 cycle to evaluate MRD status) or within 3 days before Cycle 17 Day 1 visit, subjects will be randomized based on their MRD status. Randomization will occur via Interactive Response Technology (IRT) or alternative system provided by the Sponsor.

MRD-neg subjects will be randomized to either **ibrutinib or placebo**, and therapy should be continued until MRD-positive relapse, disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

Subjects not obtaining confirmed MRD-neg responses (considered MRD-pos) will be randomized to either **ibrutinib + venetoclax or ibrutinib alone**. Ibrutinib and/or venetoclax should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

Central labs for MRD assessment will be used to inform randomization strata, and re-introduction of therapy. Local labs will be used to guide all other dosing-related decisions. In the event of rising MRD assessments, or of clinically suspected disease progression, the subject should continue to receive study medication, at the discretion of the Investigator, until MRD-positive relapse or disease progression is confirmed respectively.

8.2.2. Cycle 17 Randomization Visit and Every 3 Cycles Thereafter

The following procedures will be performed on Day 1 (±3 days) of Cycles 17 and every 3 cycles thereafter (unless indicated otherwise) until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2:

Pre-Dose

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- CT/MRI (Cycle 23, Cycle 29, Cycle 35 and then annually thereafter)
- Overall response assessment
- Bone marrow biopsy (±14 days from C29 unless collected prior for CR assessment, and confirmed MRD-negative in BM)
- MRD assessment (by PB starting Cycle 20, 23, 26, 29 and every 6 cycles thereafter; by bone marrow aspirate [BMA] at Cycle 29 in randomized subjects, and in any subject with MRD-neg conversion in PB; BMA can be drawn ±14 days from C29D1.)
- [redacted] assays [redacted]

Post-Dose

- Dispense randomization specific study medication to subject for off-site use and provide study drug compliance instructions

8.2.3. Suspected MRD-positive Relapse Visit (Any Time)

If MRD-positive relapse is suspected, subject should return to clinic as soon as possible and the following procedures will be performed:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Overall response assessment
- MRD assessment (by PB)
- [redacted] assays

8.3. Fixed Duration Cohort

Fixed Duration Cohort: Treatment

The Schedule of Assessments (Appendix B. summarizes the frequency and timing of efficacy, [redacted] and safety measurements applicable to this study. The timing of all 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.

Following completion of the Screening visit and once eligibility has been confirmed (per inclusion/exclusion criteria), subjects will initiate ibrutinib treatment. Venetoclax will be added to ibrutinib treatment and initiated after completion of 3 cycles of ibrutinib. The venetoclax dose will be ramped up over 5 weeks per standard dosing recommendations (see Section 5.3 for ibrutinib and venetoclax dosing).

After completion of 15 cycles of treatment, subjects will come off treatment and will continue to be followed for efficacy. Subjects that are unable to complete all 12 cycles of combination therapy will continue to follow the same visit schedule until disease progression. After disease progression, subjects will enter the Post-PD Follow up Phase (Section 8.9).

8.3.1. Treatment Visits

8.3.1.1. 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 enroll subject. Dosing should occur within 3 days of confirmation.
- Adverse events
- Physical examination
- Vital signs
- ECOG performance status
- Concomitant medications
- Hematology
- Serum chemistry (including creatinine clearance)
- β_2-microglobulin
- Tumor Lysis Risk assessment (use Screening CT and C1D1 ALC. see Appendix H for risk assessment categories)

- [redacted] assays
- IGHV - will be derived from a [redacted] sample (if IGHV result is not informative for any reason, another peripheral blood sample should be drawn and sent to the central lab at the next appropriate timepoint)
- FISH panel
- Karyotype
- MRD in peripheral blood
- Perform urine pregnancy test for women of childbearing potential only

Dosing and Post First Dose

- In-clinic administration of ibrutinib
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.3.1.2. Cycles 2 and 3 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of each cycle (except for CT/MRI):

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- CT/MRI (to assess response and lymph node sum of the product of the diameters [SPD] for TLS risk assessment, Cycle 3 only – to be obtained as close to the beginning of Cycle 4 as possible, while still allowing for appropriate TLS risk-guided interventions including hospitalization if appropriate)
- Hematology
- Serum chemistry

Dosing and Post-Dose

- In-clinic administration of ibrutinib (Cycle 2 only)
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.3.1.3. Cycle 4 Visits

8.3.1.3.1. Pre-Cycle 4 (Pre-initiation of Venetoclax)

The following procedures will be performed 2-3 days (±3 days) prior to Cycle 4:

- Overall response assessment
- Hematology
- Serum Chemistry
- [redacted] assays [redacted]
- Tumor Lysis Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk)

The following procedures will be performed 1 day prior to Cycle 4:

- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk)

8.3.1.3.2. Cycle 4 Week 1 Day 1

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycle 4, Week 1:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk, venetoclax administration setting, and frequency of serum chemistry monitoring assessments)

Dosing and Post First Dose of Venetoclax

- In-clinic administration of ibrutinib
- In-clinic administration of venetoclax 20 mg for low and medium risk TLS subjects
- Consider hospitalization for first dose of venetoclax 20 mg in medium risk TLS subjects with a CrCl < 80 mL/min
- In-hospital administration of first dose of venetoclax 20 mg for high risk TLS subjects
- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.3.1.3.3. Cycle 4 Week 1 Day 2

Pre-Dose

- Adverse events
- Hematology
- Serum chemistry
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

8.3.1.3.4. Cycle 4 (Week 2 – Week 4) Visits

The following procedures will be performed on Day 1 (±3 days) of Cycle 4, Weeks 2, 3, and 4 (coincides with venetoclax standard dose ramp-up of 50 mg (W2D1), 100 mg (W3D1), and 200 mg (W4D1):

Pre-Dose

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Syndrome Risk assessment (see Appendix H for risk assessment categories)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

Dosing and Post-Dose

- In-clinic administration of venetoclax 50 mg (Week 2), 100 mg (Week 3) and 200 mg (Week 4) for low and medium TLS risk subjects
- Consider hospitalization for first dose of venetoclax 50 mg in medium risk TLS subjects with a CrCl < 80 mL/min
- In-hospital administration of first dose of venetoclax 50 mg dose at Week 2 for high risk TLS subjects; in-clinic administration of venetoclax 100 mg (Week 3) and 200 mg (Week 4) for high risk TLS subjects
- Dispense venetoclax for offsite use and provide study drug compliance instructions

8.3.1.3.5. Cycle 4 Week 2 Day 2

Pre-Dose

- Adverse events
- Hematology
- Serum chemistry
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk and frequency of serum chemistry monitoring assessments)

8.3.1.4. Cycle 5 Visits

8.3.1.4.1. Cycle 5 Week 1 and Week 3 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycle 5, Week 1 and Week 3:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- Creatinine clearance (Cockcroft-Gault)
- Tumor Lysis Syndrome Risk assessment (see Appendix H for risk assessment categories) (Week 1 Only)
- Tumor Lysis Syndrome prophylaxis (see Section 5.4.2.2 for prophylaxis schedule based on risk, venetoclax administration setting, and frequency of serum chemistry monitoring assessments) (Week 1 Only)

Dosing and Post-Dose

- In-clinic administration of venetoclax
- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions (Week 1 only)

8.3.1.5. Cycle 6 – Cycle 9 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycles 6, 7, 8, and 9:

- Adverse events
- Concomitant medication
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- CT/MRI (Cycle 7 only)
- Overall response assessment (Cycle 7 only)
- MRD assessment (in peripheral blood Cycle 7 only)

Dosing and Post-Dose

- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.3.1.6. Cycle 10 and Cycle 13 Visits

Pre-Dose

The following procedures will be performed on Day 1 (±3 days) of Cycles 10 and 13:

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- β_2-microglobulin (at Cycle 10 only)
- CT/MRI (C10 and C13)
- Overall response assessment (by imaging C10 and C13)
- MRD assessment (in peripheral blood)

- Bone marrow aspirate and biopsy (C10). Bone marrow MRD should be assessed whenever a BM aspirate is collected. Bone marrow can be collected ±14 days from scheduled C10D1.

Post-Dose

- Dispense ibrutinib and venetoclax for offsite use and provide study drug compliance instructions

8.3.2. Fixed Duration Cohort: Post treatment visits

For subjects who complete all 15 cycles of fixed duration regimen, the following procedures will be performed on Day 1 (±3 days) of Cycles 19 (Post Completion of Cycle 15 therapy), 25, 28, 31 and every 6 months thereafter (or as indicated below) until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2.

Subjects who discontinue treatment before completing the fixed duration regimen will continue to come in for response follow-up visits per schedule until confirmed disease progression.

- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistries
- CT/MRI (Cycle 19, Cycle 25, Cycle 31, and annually thereafter)
- Overall response assessment
- MRD assessment (by PB at Cycle 19, 25, 28*, 31, and annually thereafter; by PB and BMA at Cycle 19; BMA can be drawn ±14 days from C19D1) :
- Bone Marrow Biopsy (Cycle 19 only)
- [redacted] assays [redacted]
- * NOTE: Cycle 28 MRD collection is not required for patients who have completed these respective visits prior to Amendment 3 site approval and any required reconsent

8.4. Reintroduction of Study Drug (MRD and FD Cohorts)

Subjects in the MRD cohort who are randomized and subjects in the Fixed Duration cohort who complete the fixed duration treatment may have study drug reintroduced if they become MRD positive (MRD cohort) or have confirmed progressive disease (either cohort).

Imaging for restaging is required prior to reintroduction. Medical Monitor approval is required prior to reintroduction of any study drug.

Creatinine clearance, Coagulation panel (PT/INR, aPTT) (for ibrutinib reintroduction), IGHV, karyotype, FISH, and [redacted] will be assessed at the first reintroduction visit. The following

procedures will be performed prior to reintroduction, and every 4 months for the first year, then every 6 months until PD, unless otherwise indicated.

- Physical exam
- Vital signs
- Hematology
- Serum chemistry
- CT/MRI (prior to reintroduction, at 4 months, 12 months, and annually thereafter)
- Overall response assessessments
- Adverse events
- Concomitant medications
- Study drug compliance review
- Bone Marrow assessment (only at visit if needed to confirm CR, or if clinically indicated to confirm PD)
- [redacted] Assay [redacted]

Subjects will follow the schedule for their retreatment as outlined in Appendix C, Appendix D, and Appendix E. Retreatment with ibrutinib or venetoclax or combination can be continued for the duration indicated, until disease progression as determined by investigator or until they meet criteria for withdrawal in Section 9.2. Subjects must meet all of the criteria for reintroduction listed below.

Criteria for Reintroduction of Study Drug

Inclusions

1. ECOG Performance Status ≤2
2. Platelet count >30,000/µL (30,000 cells/mm^3 or 30 x 10^9/L)
3. Adequate hepatic and renal function defined as:
   a) Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN)
   b) Creatinine Clearance (CrCl) ≥60 mL/min (eg, as estimated by Cockcroft-Gault)
   c) Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
4. Prothrombin time (PT)/International normal ratio (INR) <1.5 x (upper limit of normal) ULN and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).
5. Female subjects of reproductive potential must have a negative serum pregnancy test upon study entry.

6. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (eg, condom, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug. Male subjects must agree to refrain from sperm donation until 90 days after the last dose of study drug.

Exclusions

1. Development 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 the 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
2. Known or suspected history of Richter's transformation.
3. Recent infection requiring systemic treatment that is ongoing or any uncontrolled active systemic infection.
4. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
5. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety.
6. 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.
7. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix G).
8. Currently active, clinically significant hepatic impairment Child-Pugh Class B or C according to the Child Pugh classification (Appendix K).
9. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura, or the need for daily prednisone >20 mg daily (or corticosteroid equivalent) to treat or control the autoimmune disease.

Categories of Reintroduction

Ibrutinib: Appendix C

- Subjects in the MRD cohort who are MRD-negative and have been randomized to placebo; OR

- Subjects in the Fixed Duration cohort who have completed the fixed duration of treatment.

Venetoclax: Appendix D

- Subjects in the MRD cohort who are MRD-positive and have been randomized to ibrutinib only; OR
- Subjects in the MRD cohort who are in MRD-negative arms and have previously had ibrutinib reintroduced.

Ibrutinib + venetoclax: Appendix E

- Subjects in the Fixed Duration cohort who have completed the fixed duration of treatment (subjects will take combination for the same fixed duration in the protocol [15 months]).

8.5. Suspected PD Visit (Any Time)

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

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- CT/MRI scan (For confirmation of PD)
- Bone marrow biopsy/aspirate as clinically indicated
- Overall response assessment
- Hematology
- Serum chemistry
- [redacted] assays (MRD and FD cohort, including with bone marrow biopsy when obtained)

8.6. Suspected CR Visit

The following procedures will be performed (along with regularly scheduled study assessments) when Complete Response by imaging is suspected:

- Bone marrow biopsy and aspirate (for CR confirmation)
- [redacted] assays (MRD cohort only)
- MRD assessment (by PB and bone marrow aspirate)

8.7. 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) or at start of new anticancer therapy, whichever occurs earlier. For the Fixed Duration Cohort, if subject completes fixed duration regimen, this visit will take place at Cycle 17 Day 1.

- Adverse events
- Concomitant medications
- Study drug compliance review
- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum chemistry
- MRD (peripheral blood)
- [redacted] assays (MRD cohort only)

Subjects that withdraw from treatment for reasons other than clinical progressive disease in either cohort should continue to participate in ongoing Response Follow-Up visits until confirmed disease progression.

8.8. Response Follow-Up Visits

Subjects who discontinue treatment for reasons other than disease progression will continue to come in every 3 months (or per assigned treatment schedule) until disease progression or study closure, whichever is earlier. Subjects will undergo the following procedures:

- Physical exam
- Vital signs
- ECOG
- Hematology
- Serum Chemistry
- MRD (peripheral blood) every 6 months for one year, then annually thereafter until initiation of subsequent anti-cancer therapy
- Overall Response Assessment
- CT/MRI scan (every 6 months)
- Other malignancies
- Any subsequent anti-cancer therapy

If an alternative anti-cancer therapy is initiated, response to all subsequent anti-cancer therapies including best overall response for each regimen, whether the subject progressed following each regimen, and date of PD if applicable will be assessed.

8.9. Post-PD Follow-Up Phase

Once subjects experience disease progression and discontinue study treatment, they will be contacted approximately every 3 months (±14 days), or as needed, by clinic visit or telephone to assess survival and the use of alternative anti-cancer therapy (response to all subsequent anti-cancer 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.

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:

- Confirmed progressive disease
- Unacceptable toxicity: an intercurrent illness or AE that prevents further study drug 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

Subjects in the Randomization Phase of the MRD cohort or subjects in the Fixed Duration cohort who elect to not reintroduce therapy after confirmed PD, or have a confirmed PD after reintroduction of therapy, will be withdrawn from study treatment.

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

The investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib and/or venetoclax treatment due to disease progression and should provide documentation of disease progression for review by the Sponsor's Medical Monitor. If a subject shows signs of

disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

9.3. Withdrawal from Study

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

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

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

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details including the testing procedure for the secondary endpoints will be provided in the Statistical Analysis Plan (SAP).

10.1. Subject Information

The analysis populations are defined as:

All treated populations: defined as all enrolled subjects who received at least 1 dose of study drug in either the MRD cohort or the Fixed Duration cohort and will be used in both efficacy and safety analysis.

MRD-negative randomized population: defined as all subjects in the MRD cohort who achieve confirmed MRD-negative response at the end of the pre-randomization phase and are randomized to either placebo arm or ibrutinib arm for the double-blind treatment. Subjects in this population will be analyzed according to the treatment to which they are randomized.

MRD-positive randomized population: defined as all subjects in the MRD cohort who do not achieve confirmed MRD-negative response at the end of the pre-randomization phase and are randomized to either single-agent ibrutinib arm or ibrutinib + venetoclax combination treatment arm for a prolonged open label treatment. Subjects in this population will be analyzed according to the treatment to which they are randomized.

Pharmacokinetic-evaluable population: defined as all enrolled subjects who received at least 1 dose of study drug and had at least 1 pharmacokinetic sample obtained post-treatment in pre-randomization phase.

[redacted] **population:** defined as all enrolled subjects whose [redacted] is available.

10.2. Endpoints

10.2.1. MRD Cohort:

Primary Endpoint:

- 1-year disease-free rate in MRD-negative randomized subjects

Secondary Endpoints:

- MRD-negative response rate
- Overall response rate
- Complete response rate (CR / CRi)
- Duration of response
- TLS risk reduction
- Progression free survival
- Overall survival
- Pharmacokinetics of ibrutinib and venetoclax when dosed in combination
- Safety and tolerability

Exploratory Endpoints:

- [redacted]

10.2.2. Fixed Duration Cohort:

Primary Endpoint:

- Complete response (CR/CRi) rate

Secondary Endpoints:

- Duration of response
- MRD-negative response rate
- Overall response rate
- TLS risk reduction
- Progression free survival
- Overall survival
- Safety and tolerability

Exploratory Endpoints:

- [redacted]
- [redacted]
- [redacted]

10.3. Sample Size Determination

MRD Cohort

The study will be powered based on the primary endpoint of randomization phase, 1-year disease-free rate in MRD-negative randomized subjects (ibrutinib vs placebo). The total sample size will be based on both MRD-negativity clinical response rate from the Pre-randomization Phase and the sample size assumption from Randomization Phase.

Sixty randomized subjects with confirmed MRD-negative status will provide approximately 80% power to detect a 30% improvement in the 1-year disease-free rate, assuming the 1-year disease-free rate is 60% for the control (placebo) arm, at a 2-sided significant level of 0.05.

Assuming a 40% MRD-negative response rate for the ibrutinib and venetoclax combination therapy in the Pre-randomization Phase, 150 subjects will be enrolled in the Pre-randomization Phase in order to have 60 subjects achieve confirmed MRD-negative response and to be randomized. Final sample size may be adjusted based on an early assessment of the MRD-negative response rate among the first 30 subjects who complete 9 cycles of treatment in Pre-randomization Phase (See section 3.1.1).

Fixed Duration Cohort

Assuming the CR rate for ibrutinib + venetoclax is 50%, 125 subjects without del 17p will provide 83% power to ensure the rate is > 37% at 1-side alpha 0.025. A CR rate of 50% would represent meaningful improvement compared to the CR rate seen with the fixed duration combination of bendamustine + rituximab (31%), and would be an improvement over the CR rate seen with the standard of care fixed duration regimen fludarabine, cyclophosphamide and

rituximab (40%) which were obtained in the CLL10 study, which included only patients without del 17p (Eichhorst 2016).

10.4. Efficacy Analysis

In general, the MRD cohort and the Fixed Duration cohort will be analyzed separately. Analysis details will be provided in the SAP.

Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, the number of observations, means, standard deviations, medians, and ranges will be reported. For discrete variables, frequency will be summarized and the 95% confidence interval will be estimated. For time-to-event variables, Kaplan-Meier estimates will be provided. No inferential tests will be performed for pre-randomization phase. The primary endpoint, 1-year disease-free rate in MRD-negative randomized subjects, will be tested between placebo and ibrutinib arms at a 2-sided alpha level of 0.05 All the stratified analyses will be based on the randomization stratification factors, immunoglobulin heavy-chain variable region (IGHV) status.

10.4.1. MRD-Negative Response Rate

MRD-negative response rate is defined as the proportion of subjects who achieve MRD-negativity (definition in Section 7.2.1.4).

In the MRD cohort, and the Fixed Duration cohort, MRD-negative response rate is the secondary endpoint. The analysis of MRD negativity will be based on the all treated population. [redacted] will be summarized as an exploratory analysis.

10.4.2. Disease-Free Survival (DFS)

Disease-free survival (DFS) is the primary endpoint for randomization phase of the MRD cohort and will be analyzed in MRD-negative randomized subjects. DFS is defined as the time that subjects remain in MRD-negative status without meeting MRD-positive relapse criteria (definition in Section 7.2.1.4.2), or disease progression (assessed by investigator per IWCLL 2008 criteria) or death from any cause. The primary analysis will be performed when all randomized subjects have had the opportunity to complete at least 12 cycles of randomized treatment or follow-up. 1-year and 2-year disease-free survival rate will be explored. Analysis details will be provided in the SAP.

10.4.3. Overall Response Rate (ORR)

Overall response rate (ORR) is defined as the proportion of subjects who achieve a CR, CRi, nPR, PR, or PRL as evaluated by investigator using IWCLL 2008 criteria. Subjects who do not have any post-baseline response assessment will be considered as non-responders. It is a secondary endpoint for the MRD cohort and the Fixed Duration cohort. [redacted] as exploratory endpoints. A pooled

analysis in combination with another dataset (eg, CLL3011; GLOW) may be performed for ibrutinib retreatment. Details of the statistical analysis will be described in a separate SAP as applicable.

10.4.4. Complete Response Rate (CRR)

Complete response rate (CRR) is defined as the proportion of subjects who achieve a CR or CRi as evaluated by investigator using IWCLL 2008 criteria. Subjects who do not have any post-baseline response assessment will be considered as non-responders. It is the primary endpoint for the Fixed Duration cohort, and secondary endpoint for the MRD cohort and will be summarized in the all treated population.

10.4.5. Duration of Response (DOR)

Duration of response will be calculated for subjects achieving a response (CR, CRi, nPR, PR) based on IWCLL response criteria and defined as the interval between the date of initial documentation of a response including PR with lymphocytosis, until disease progression or death from any cause, whichever occurs first. Kaplan-Meyer methodology will be used to estimate event-free curves, median and landmark estimates.

10.4.6. Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from the first dose date of study treatment until disease progression (per IWCLL 2008 criteria) or death from any cause, whichever occurs first.

In the MRD cohort and the Fixed Duration cohort, PFS is a secondary endpoint and will be analyzed in the all treated population. Distribution of PFS will be estimated using Kaplan-Meier method. Median PFS, landmark estimates and their corresponding 95% CI will be provided.

10.4.7. Overall Survival (OS)

Overall survival (OS) is defined as the time from the first dose date of study treatment until date of death due to any cause.

In the MRD cohort, and the Fixed Duration cohort, OS is a secondary endpoint and will be analyzed in the all treated population. Distribution of OS will be estimated using Kaplan-Meier method. Median OS, landmark estimates and their corresponding 95% CI will be provided.

10.4.8. Tumor Lysis Syndrome (TLS) Risk Reduction Rate

TLS risk reduction rate is defined as the reduction in the proportion of subjects who are at high risk of TLS after the 3-cycle lead-in of single agent ibrutinib, compared to the proportion of patients who are at high risk of TLS at baseline. A reduction in TLS risk from high risk to medium or low risk is clinically meaningful because there is a reduction in the extent of TLS

monitoring and risk of hospitalization. TLS risk category is defined in the protocol in Table 3, where Tumor Burden category is equated to TLS risk category. TLS risk reduction is a secondary endpoint for the MRD cohort and the FD cohort, and will be summarized in the all treated population.

10.4.9. [redacted]

[redacted]

This is an exploratory endpoint in the MRD cohort and the Fixed Duration cohort. It will be analyzed in all treated population.

10.4.10. [redacted]

[redacted] This is an exploratory endpoint in the MRD cohort and the Fixed Duration cohort. It will be analyzed in all treated population.

10.4.11. Safety Analysis

In the MRD cohort, analysis of safety data will be conducted on the all treated population in pre-randomization phase and safety population in the randomization phase. An overall summary across both pre-randomization and randomization phase may also be provided as appropriate. The baseline value is defined as the last value collected on or prior to the first dose date of study drug. In the Fixed Duration cohort, safety analysis will be based on all treated population.

The safety variables to be analyzed include exposure of study drugs, AEs, clinical laboratory test results (hematology and chemistry), ECOG performance, physical examination, and vital signs measurements. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent period is defined as the period of time from the first dose of study treatment, until the earlier of:

- Thirty days following the last dose of ibrutinib or 30days following the last dose of venetoclax, whichever occurs later

AND

- The start date of a new anti-cancer therapy.

The treatment-emergent AEs (TEAEs) are those events that:

- Are not present prior to the treatment-emergent period and occur during the treatment-emergent period,
- The onset dates are missing, and end dates are during the treatment-emergent period,
- Are considered related to study drug by the investigator regardless of the start dates of the events, or
- Are present prior to the treatment-emergent period but worsen in severity during the treatment-emergent period or are subsequently considered related to study drug by the investigator.

All treatment-emergent AEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (CTCAE, v4.03) or IWCLL for hematologic toxicity, and drug relationship, as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or a SAE.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be standardized using the International System SI unit. Selected hematologic and chemistry laboratory parameters are detailed in Section 7.1.2. Hematologic parameters including platelet counts, hemoglobin, and neutrophils will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL 2008 guidelines. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03.

Unless otherwise specified, only baseline and post-baseline lab values collected during the treatment-emergent period will be included in the analysis. Descriptive statistics will be used.

For selected laboratory parameters, the worst post baseline toxicity grade will be summarized. Analysis for hepatic impairment and renal impairment will be provided.

10.5. Pharmacokinetic Analysis

10.5.1. Ibrutinib

Ibrutinib and PCI-45227 bioanalytical data will be used in noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including, but not limited to: C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$) at each dosing interval.

Individual and mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

Ibrutinib data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population-PK analysis using nonlinear mixed effects models. For the population-PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population-PK analyses (if performed) will be presented in a separate report.

Steady-state ibrutinib PK data when administered alone in the lead in period will be compared to the data when administered in combination with venetoclax to explore the potential for a pharmacokinetic interaction between ibrutinib in combination use with venetoclax.

Ibrutinib model-derived exposure parameters (PK parameters) may be used to explore PK/PD correlation between the exposure of ibrutinib with relevant clinical [redacted] information to assess effectiveness and toxicity.

10.5.2. Venetoclax

Venetoclax bioanalytical data will be used in noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize venetoclax concentrations at each sampling time point and PK parameters (including, but not limited to: C_{max}, T_{max}, and AUC) at each dosing interval.

Individual and mean plasma venetoclax concentration time profiles will be plotted.

Venetoclax data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population-PK analysis using nonlinear mixed effects models. For the population-PK analysis, covariates that could

potentially correlate with plasma PK parameters will be evaluated. The results of the population-PK analyses (if performed) will be presented in a separate report.

Venetoclax model-derived exposure parameters (PK parameters) may be used to explore PK/PD correlation between the exposure of venetoclax with relevant clinical [redacted] information to assess effectiveness and toxicity.

10.6. [redacted]

[redacted] Descriptive statistics will be used to summarize these exploratory endpoints. The detail will be given in SAP. Results will be presented in a separate report.

10.7. Data Review Committee (DRC)

A DRC will be established to monitor data in the MRD Cohort Safety Run-in Period (defined as the date of first dose of ibrutinib at Cycle 1 Day 1 through the DLT evaluation period) to ensure the safety of the subjects enrolled in this novel combination study. The committee will meet periodically to review safety data. After the review of the first 6 evaluable subjects who have completed the combination of ibrutinib + dose ramp-up of venetoclax with an additional week of follow up, the DRC may make recommendations regarding the recommended doses and continuation of the study. A follow-up DRC review will occur after all subjects in the Safety Run-in Period have either discontinued therapy and/or have completed the venetoclax dose ramp up and 1 week follow up, then the DRC may make additional recommendations regarding the recommended doses.

The DRC will consist of the Medical Monitor or designee, a Drug Safety representative, a biostatistician, and at least 2 participating Investigators.

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 AE term. As an example, "worsening of CLL/SLL" 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 ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalization required per protocol for subjects at high risk for TLS (high tumor burden, or those with CrCl <80 mL/min) are not considered AEs unless the hospitalization is prolonged >24 hours or if additional intervention, not described as mandatory prophylaxis in Table 3, is required. Elective hospitalizations for social reasons, solely for the administration of therapy, 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 (SAE) based on International Conference on Harmonisation (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 unplanned in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

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

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Hematologic Adverse Event Grading Scheme (Hallek 2008) will be used for grading the severity of hematologic AEs. Refer to Appendix L for the grading of hematologic AEs.

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. 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 IB/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 IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB 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 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 AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event 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 AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during subject office visits, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the AEs eCRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE 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. Adverse events noted during Screening period will be recorded in Medical History CRF. SAEs will be reported to the Sponsor on the SAE Report Form from the time of ICF signing until 30 days following the last dose of study drug. 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. In the case of subjects who are transferring their ibrutinib treatment from this protocol to another ibrutinib treatment protocol, AE collection under this protocol will stop at the time AE collection starts under the next protocol.

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. In the case of subjects who are transferring their ibrutinib treatment from this protocol to another ibrutinib treatment protocol, SAE collection under this protocol will stop at the time SAE collection starts under the next protocol.

Adverse event and SAE collection will also stop at the time any subject starts a subsequent anticancer treatment within the first 30 days after discontinuing ibrutinib.

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 AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must assess the relationship of the AE/SAE to the study therapy and record their opinion in the CRF. All measures required for AE/SAE 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 SAE.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs/SAEs 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, or a female partner of a male 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 study drug. 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 study drug. 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 AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 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 SAE.

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 AEs, or groups of AEs, 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 ICF 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 Food and Drug Administration (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 case report forms (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

The case report forms 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, placebo and venetoclax 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, placebo or venetoclax 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, placebo and venetoclax 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-1142-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib/placebo dispensed for that subject

4. Lot number(s) of venetoclax dispensed for that subject
5. Date and quantity of drug(s) dispensed
6. Any unused drug(s) 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 will be performed by the monitor if allowed by institutional policy.

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. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. 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 is 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 sub-investigator (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.

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 for MRD cohort

Study Visits	Screening Period	Pre-Randomization Phase (1 cycle = 28 days)											Once MRD Status Confirmed Post C16, Proceed to Randomization C17	Suspected CR
		Cycle 1	Cycle 2 & 3	Cycle 4					Cycle 5	Cycles 6-9	Cycles 10 & 13	Cycle 16		
				Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3					
		D1 (baseline)[a]	D1	D-3 or D-2	D-1	D1	D2	D1	D1	D1	D1	D1		
Study Visit Windows	-30 days	± 3 days		± 3 days (minimum of 7 days at each dose level of venetoclax)						± 3 days				
Study Drug Administration and Dispensation														
both ibrutinib		**ibrutinib:** 420 mg PO daily[b]												
and venetoclax						**venetoclax:** dose ramp up[c]			**venetoclax:** 400 mg PO daily[c]					
Procedures														
Informed consent	X													
Medical history	X													
Confirm eligibility[d]		X												
Concomitant medications	X	X	X			X		X	X	X	X	X		
Adverse events[e]	X	X	X			X	X	X	X	X	X	X		
Study drug compliance review[f]		X	X			X		X	X	X	X	X		
Height[g]	X													
Physical exam, vital signs, weight, ECOG[g]	X	X	X			X		X	X	X	X	X		
Pregnancy[k]	X (serum)	X (urine)												
Overall response assessment				X						X C7	X	X		
CT/MRI scan	X[h]		X[h] C3								X C10	X		
Bone marrow biopsy/aspirate for clinical response (local lab and [redacted] central lab))	X[i]											X[i]		X[i]
Bone marrow aspirate for [redacted] (central lab)	X[i]													
Minimal Residual Disease assessment (MRD central lab) [j]		X (PB)								X C7 (PB)	X (PB)	X (BMA & PB)		X (BMA & PB)
Tumor Lysis Syndrome (TLS) Risk Assessments[q]		X		X		X		X	X Wk1					
Tumor Lysis Syndrome Prophylaxis				X	X	X	X	X	X Wk1					

Appendix A. Schedule of Assessments for MRD cohort - (Cont.)

Study Visits	Screening Period	Pre-Randomization Phase (1 cycle = 28 days)												Suspected CR
		Cycle 1	Cycle 2 & 3	Cycle 4					Cycle 5	Cycles 6-9	Cycles 10 & 13	Cycle 16	Once MRD Status Confirmed Post C16, Proceed to Randomization C17	
				Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3					
		D1 (baseline)[a]	D1	D-3 or D-2	D-1	D1	D2	D1	D1	D1	D1	D1		
Procedures (continued)														
Hematology[k]	X	X	X	X		X[u]	X	X[u]	X[u]	X	X	X		
Serum chemistry[k]	X	X	X	X		X[u]	X	X[u]	X[u]	X	X	X		
Creatinine clearance (eg Cockcroft-Gault)[k]	X	X				X		X	X					
Hepatitis serologies[k]	X													
Coagulation panel[k]	X													
Buccal Swab		X												
FISH (local or central lab)[l]		X												
Karyotype[w]		X (PB)												
IGHV[m]		X												
[redacted] Assays														
12-lead ECG[n]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)												
Substudies														
PK sample collection[o,p]			X C2							X C6				

Appendix A. Schedule of Assessments - (Cont.)

			Randomization Phase					
			(1 cycle = 28 days)	Suspected MRD-positive	Suspected PD[s]	End-of-Treatment	Response Follow-Up	Post PD Follow Up
Study Visits		Randomi-zation	Cycles 17 until disease progression (every 3 cycles)	As soon as possible after MRD-positive relapse	As soon as possible after suspected PD	30 Days [v]	Every 3 months	Every 3 months
Study Visit Windows		within 3 days before C17D1	± 3 days	Any time	Any time	± 3 days	± 14 days	± 14 days
	Study Drug Administration and Dispensation							
MRD-NEG CONFIRMED (Double-Blind)	ibrutinib or		**ibrutinib**: 420 mg PO daily ⇨	Add venetoclax[t]				
	placebo		**placebo**: 3 capsules PO daily ⇨	Add ibrutinib[t]				
MRD-POS CONFIRMED (Open-label)	ibrutinib or		**ibrutinib**: 420 mg PO daily ⇨		Add venetoclax[t]			
	ibrutinib + venetoclax		**ibrutinib**: 420 mg PO daily **venetoclax:** 400 mg PO daily ⇨	Investigators choice				
	Procedures							
Confirm MRD status and randomize		X						
Concomitant medications			X	X	X	X		
Adverse events[e]			X	X	X	X		
Study drug compliance review[f]			X	X	X	X		
Height								
Physical exam, vital signs, weight, ECOG[g]			X	X	X	X	X	
Overall response assessment			X	X	X		X	
CT/MRI scan			X C23, C29, C35 and annually thereafter		X		X every 6 months	
Bone marrow biopsy/aspirate for clinical response (local lab and [redacted] central lab)[i]			X (C29 only)		X (if clinically indicated)			
MRD assessment (MRD central lab) [j]			X (PB)[j], X (C29 BMA)[j] C20, C23, C26, C29 then every 6 cycles thereafter	X (PB)		X (PB)	X	
Hematology[lk]			X	X	X	X	X	
Serum chemistry[lk]			X	X	X	X	X	
[redacted] Assays		[redacted]						
12-lead ECG[n]			If clinically indicated (eg, subjects with palpitations, lightheadedness)					

Appendix A. Schedule of Assessments - (Cont.)

		Randomization Phase					
		(1 cycle = 28 days)	Suspected MRD-positive	Suspected PD[s]	End-of-Treatment	Response Follow-Up	Post PD Follow Up
Study Visits	Randomi-zation	Cycles 17 until disease progression (every 3 cycles)	As soon as possible after MRD-positive relapse	As soon as possible after suspected PD	30 Days [v]	Every 3 months	Every 3 months
Survival, including other malignancies						X (other malignancies)	X
Any new anti-cancer therapy						X	X

Footnote:

a. Cycle 1 D1: To be collected pre-dose or within +/- 3 days, unless otherwise specified.

b. Ibrutinib: Day 1 dose of Cycle 1, Cycle 2, Cycles 4 and Cycle 6 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

c. Venetoclax: Day 1 dose of Cycle 4 Weeks 1-4, Cycle 5 Week 1 and Cycle 6 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

d. Confirmation of eligibility and enrollment may occur within 3 days of Day 1 of Cycle 1.

e. Adverse Events: AEs are reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. AEs that occur prior to first dose should be entered as Medical History. 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.

f. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration.

g. Physical Exam: Height will only be collected in the Screening Period. Vital signs will be collected through end of treatment only. ECOG collected through disease progression.

h. CT Scan: Baseline CT scan can be performed up to 6 weeks prior to enrollment. Cycle 3 CT scan should be performed and assessed prior to starting venetoclax at Cycle 4 and are obtained for TLS risk assessment. Cycle 3 CT scans should be obtained as close to the beginning of Cycle 4 as possible, while still allowing for appropriate TLS risk-guided interventions including hospitalizations if appropriate. Please reference section 7.1.3.2 for details.

i. Bone marrow biopsy: should be performed at Screening or up to 90 days before the first dose of study drug before enrollment, Cycle 16 (±14 days) [unless collected prior for CR assessment, and confirmed MRD-negative in BM], Cycle 29 (±14 days), and as needed to confirm complete response (CR) or evaluate cytopenia. All bone marrow biopsies will be assessed by local laboratory. A portion of bone marrow biopsies collected at [redacted] should be sent to [redacted] central lab. An additional bone marrow sample will be sent to central laboratory for karyotype (if ALC ≤ 4000) if BM was collected within 90 days prior to screening and at Day 1 of reintroduction of study drug (see section 7.1.3.5). Bone marrow aspirate for [redacted] will be derived from MRD bone marrow aspirate, no additional sample needs to be collected.

j. MRD Assessment: should be performed in peripheral blood (PB) at Cycle 1, Cycle 7, 10, 13, 16, 20, 23, 26, 29 and every 6 cycles thereafter. MRD assessment confirmation by both peripheral blood and bone marrow aspirate (BMA) will be performed at Cycle 16 (±14 days). An additional BMA (after

suspected CR or C16) can be collected in consented subjects prior to randomization to serially confirm MRD-negativity in the bone marrow compartment. For all randomized subjects, and any subjects with MRD-neg conversion in PB, an additional BMA should be collected at Cycle 29 (±14 days).

k. Local labs: Hematology, chemistry, Creatinine Clearance, Hepatitis serologies (see Section 7.1.2.4), serum and urine pregnancy and Coagulation panel may be performed at local labs.

l. Cytogenetics, FISH panel: If local lab FISH results are not available or if site cannot perform del17p and del11q testing, sample should be sent to Central Lab.

m. IGHV: Send to central lab at Cycle 1. If IGHV sample is not informative for any reason, another peripheral blood sample should be drawn and sent to the central lab at the next appropriate timepoint. Must have IGHV result in order to be randomized.

n. 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.

o. PK (ibrutinib): Day 1 of Cycle 2 and Cycle 6: to be collected pre-dose, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose. PK should only be drawn when ibrutinib is at steady state plasma levels. If any dose of ibrutinib was withheld in the week prior to C2D1 and/or C6D1, then PK assessments should be rescheduled to the next study visit day after doses have been consistently administered for ≥1 week (see Table 11).

p. PK (venetoclax): Day 1 of Cycle 6: to be collected pre-dose, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose. PK should only be drawn when venetoclax is at steady state plasma levels. If any dose of venetoclax was withheld in the week prior to C6D1, then PK assessments should be rescheduled to the next study visit day after doses have been consistently administered for ≥1 week (see Table 11).

q. Tumor Lysis Syndrome Risk Assessment: Please see Appendix H for risk assessment categories. For baseline risk assessment, use Screening CT and C1D1 ALC.

r. Tumor Lysis Syndrome Prophylaxis: Please see Section 5.4.2.2 for TLS prophylaxis schedule, venetoclax administration setting and frequency of serum chemistry monitoring assessments.

s. Suspected PD: Follow same procedures in Pre-Randomization and Randomization phases.

t. Reintroduction: Reintroduce ibrutinib (MRD-negative placebo arm) if MRD-positive relapse or IWCLL confirmed disease progression. Reintroduce venetoclax (MRD-negative ibrutinib arm) per standard dose ramp up if MRD-positive relapse or IWCLL confirmed disease progression. Reintroduce venetoclax (MRD-positive ibrutinib arm) per standard dose ramp up if IWCLL confirmed disease progression.

u. Hematology and Serum Chemistry may be collected up to 24 hours prior to each venetoclax ramp-up (Cycle 4 Weeks 2-4 and Cycle 5 Week 1), to allow for flexibility in start of ramp-up dose. Hematology and serum chemistry can be drawn on day of dosing to allow for comparisons, but results are not required before dosing decision is made. For subjects at high risk for TLS, additional hematology and serum chemistry samples will need to be collected 6-8 and 24 hours post-1st dose at Cycle 4 Weeks 3 and 4, and Cycle 5 Week 1 as part of TLS risk assessment. Please see Table 3 for serum chemistry monitoring assessments.

v. End-of-Treatment Visit: may be sooner if subject is scheduled to start a new anti-cancer treatment.

w. Karyotype: will be assessed from peripheral blood or bone marrow aspirate samples.

Appendix B. Schedule of Assessments for Fixed Duration Cohort

Study Visits	Screening Period	(1 cycle = 28 days)										
		Cycle 1	Cycle 2 & 3	Cycle 4					Cycle 5	Cycles 6-9	Cycle 10 & Cycle 13	Cycle 19 (3 cycles after completion of C15) C25, C28, C31 and every 6 months thereafter
				Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
		D1 (baseline)[a]	D1	D-3 or D-2	D-1	D1	D2	D1	D1	D1	D1	D1
Study Visit Windows	-30 days	± 3 days		± 3 days (minimum of 7 days at each dose level of venetoclax)_						± 3 days		
Study Drug Administration and Dispensation												
Ibrutinib		**ibrutinib:** 420 mg PO daily[b] until completion of C15										
Venetoclax						**venetoclax:** dose ramp up[c]			**venetoclax:** 400 mg PO daily[c] until completion of C15			
Procedures												
Informed consent	X											
Medical history	X											
Confirm eligibility[d]		X										
Concomitant medications	X	X	X			X		X	X	X	X	
Adverse events[e]	X	X	X			X	X	X	X	X	X	
Study drug compliance review[f]		X	X			X		X	X	X	X	
Height[g]	X											
Physical exam, vital signs, weight, ECOG[g]	X	X	X			X		X	X	X	X	X
Pregnancy[k]	X (serum)	X (urine)										
Overall response assessment				X						X C7	X	X C19, C25, C28, C31 and every 6 months thereafter
CT/MRI scan	X[h]		X[h] C3							X C7	X	X C19, C25, C31, and annually thereafter
Bone marrow biopsy/aspirate for clinical response (local lab and [redacted] central lab)	X[i]										X[i] C10	X[i] C19

Appendix B. Schedule of Assessments for Fixed Duration Cohort (Cont.)

Study Visits	Screening Period	(1 cycle = 28 days)										
		Cycle 1	Cycle 2 & 3	Cycle 4					Cycle 5	Cycles 6-9	Cycle 10 & Cycle 13	Cycle 19 (3 cycles after completion of C15) C25, C28, C31 and every 6 months thereafter
				Week 1		Weeks 1-2		Weeks 3-4	Wks 1 & 3			
		D1 (baseline)[a]	D1	D-3 or D-2	D-1	D1	D2	D1	D1	D1	D1	D1
Study Visit Windows	-30 days	± 3 days		± 3 days (minimum of 7 days at each dose level of venetoclax)						± 3 days		
Minimal Residual Disease assessment (MRD central lab)[j]		X (PB)								X C7 (PB)	X (PB C10 and C13, BMA C10)	X (PB & BMA C19; PB C25[t], C28[t], C31, and annually thereafter)
Tumor Lysis Syndrome (TLS) Risk Assessment[n]		X		X		X		X	X Wk1			
Tumor Lysis Syndrome Prophylaxis[o]				X	X	X	X	X	X Wk1			
Hematology[k]	X	X	X	X		X[p]	X	X[p]	X[p]	X	X	X
Serum chemistry[k,p]	X	X	X	X		X[p]	X	X[p]	X[p]	X	X	X
Creatinine clearance (eg, Cockcroft-Gault)[k]	X	X				X		X	X			
Hepatitis serologies[k]	X											
Coagulation panel[k]	X											
Procedures (continued)												
FISH (local or central lab)[l]		X[l]										
Karyotype (central lab)		X (PB)										
IGHV (central lab)[r]		X										
[redacted] Assays	[redacted]											
12-lead ECG[m]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)										

Appendix B. Schedule of Assessments for Fixed Duration Cohort - (Cont.)

Study Visits	Suspected CR As soon as possible after suspected CR	Suspected PD As soon as possible after suspected PD	End-of-Treatment [q] 30 Days	Response Follow-Up Every 3 months	Post PD Follow Up Every 3 months
Study Visit Windows	Any time	Any time	± 3 days	± 14 days	± 14 days
Procedures					
Concomitant medications		X	X		
Adverse events[e]		X	X		
Study drug compliance review[f]		X	X		
Physical exam, vital signs, weight, ECOG[g]		X	X	X	
Overall response assessment		X		X	
CT/MRI scan		X		X every 6 months	
Bone marrow biopsy/aspirate for response (local lab and [redacted] central lab)[i]	X[i]	X (if clinically indicated)			
Bone marrow aspirate for [redacted] (MRD central lab)	X[s]				
MRD assessment (MRD central lab)	X (PB & BMA)		X (PB)	X every 6 months for one year, then annually thereafter	
Hematology[k]		X	X	X	
Serum chemistry[k]		X	X	X	
[redacted] Assays	[redacted]				
Survival, including other malignancies				X (other malignancies)	X
Any new anti-cancer therapy				X	X

Footnote:

a. Cycle 1 D1: To be collected pre-dose or within +/- 3 days, unless otherwise specify

b. Ibrutinib: Day 1 dose of Cycle 1, Cycle 2, Cycle 4 and Cycle 6 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

c. Venetoclax: Day 1 dose of Cycle 4 Weeks 1-4, Cycle 5 Week 1 and Cycle 6 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

d. Confirmation of eligibility and enrollment may occur within 3 days of Day 1 of Cycle 1.

e. Adverse Events: AEs are reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. AEs that occur prior to first dose should be entered as Medical History. 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.

f. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration

g. Physical Exam: Height will only be collected in the Screening Period. Vital signs will be collected through end of treatment only. ECOG collected through disease progression.

h. CT Scan: Baseline CT scan can be performed up to 6 weeks prior to randomization. Cycle 3 CT scan should be performed and assessed prior to starting venetoclax at Cycle 4 and are obtained for TLS risk assessment. Cycle 3 CT scans should be obtained as close to the beginning of Cycle 4 as possible, while still allowing for appropriate TLS risk-guided interventions including hospitalizations if appropriate. Please reference Section 7.1.3.2 for details.

i. Bone marrow biopsy and aspirate: should be performed at Screening or up to 90 days before the first dose of study drug, Cycle 10 (±14 days), Cycle 19 (±14 days), and as needed to confirm complete response (CR) or evaluate cytopenia. All bone marrow biopsies collected will be assessed by local laboratory. A portion of bone marrow biopsies collected at [redacted] should be sent to [redacted] central lab. Bone marrow aspirate for [redacted] will be derived from MRD bone marrow aspirate, no additional sample needs to be collected.

j. MRD Assessment: should be performed in peripheral blood (PB) at Cycle 1, Cycle 7, Cycle 10, Cycle 13, End of Treatment (30 days after last dose of study drug or C17), C19 (3 months after completion of therapy), C25, C28, C31 and annually thereafter. MRD assessment confirmation by both peripheral blood and bone marrow aspirate (BMA) will be performed at Cycle 10, and C19 (3 months after completion of therapy [±14 days]). Bone marrow aspirate MRD should be performed if bone marrow is obtained to confirm CR.

k. Local labs: Hematology, chemistry (including β_2-microglobulin at C1 and C10), Creatinine Clearance, Hepatitis serologies per Section 7.1.2.4, serum and urine pregnancy and Coagulation panel may be performed at local labs.

l. Cytogenetics, FISH panel: If local lab FISH results are not available or if site cannot perform del17p and del11q testing, sample should be sent to Central Lab.

m. 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.

n. Tumor Lysis Syndrome Risk Assessment: Please see Appendix H for risk assessment categories. For baseline risk assessment, use Screening CT and C1D1 ALC.

o. Tumor Lysis Syndrome Prophylaxis: Please see Section 5.4.2.2 for TLS prophylaxis schedule, venetoclax administration setting and frequency of serum chemistry monitoring assessments.

p. Hematology and Serum Chemistry may be collected up to 24 hours prior to each venetoclax ramp-up (Cycle 4 Weeks 1-4 and Cycle 5 Week 1), to allow for flexibility in start of ramp-up dose. Hematology and serum chemistry can be drawn on day of dosing to allow for comparisons, but results are not required before dosing decision is made. For subjects at high risk for TLS, additional hematology and serum chemistry samples will need to be collected 6-8 and 24 hours post-1st dose at Cycle 4 Weeks 3 and 4, and Cycle 5 Week 1 as part of TLS risk assessment. Please see Table 3 for serum chemistry monitoring assessments.

q. End-of-Treatment Visit: Will take place at C17 for subjects who complete full fix duration of treatment. If subject discontinues treatment prior to C15, visit should take place within 30 days of last dose of study drug. Visit may occur sooner if subject is scheduled to start a new anti-cancer treatment

r. IGHV sample will be derived from one of the [redacted] samples collected

s. Bone marrow aspirate for [redacted] (central lab): [redacted] sample will be derived from bone marrow aspirate MRD sample if adequate sample available.

t. Applies only to subjects who have not yet reached this time point when Amendment 3 is approved at their site and any required reconsent.

u. Karyotype: will be assessed from peripheral blood or bone marrow aspirate samples.

Appendix C. Schedule of Assessments for Reintroduction of Ibrutinib (MRD and FD Cohorts)

Study Visits	Every 4 months for the first year, then every 6 months until PD (Day 1 of each visit)	Suspected PD (as soon as possible after suspected PD)	Post PD Follow-up (Every 4 months)
Study Visit Windows	±3 days	Any time	±14 days
Study Drug Administration and Dispensation			
ibrutinib	Ibrutinib: 420 mg PO daily		
Procedures			
Medical Monitor approval	Obtained before 1st dose		
Study Drug Compliance Review[b]	X	X	
Concomitant medications	X	X	
Adverse events[a]	X	X	
Physical exam, vital signs, weight, ECOG[c]	X	X	
Overall response assessment	X	X	
CT/MRI scan[d]	X at 4 months, 12 months and annually thereafter	X	
Bone marrow biopsy/aspirate for response (local lab and [redacted] central lab)	X (only if suspected CR / to confirm CR)	X (if clinically indicated)	
Hematology (local lab)[h]	X	X	
Serum chemistry (local lab)[h]	X	X	
Creatinine clearance (eg, Cockcroft-Gault)[h]	X (1st visit only)		
Coagulation panel[h]	X (1st visit only)		
IGHV (central lab)[f]	X (1st visit only)		
Karyotype (central lab)[g]	X (1st visit only)		
FISH (local or central lab)[e]	X (1st visit only)		
[redacted] Assays	[redacted]		
Survival status, including other malignancies			X
Any new anti-cancer therapy			X

Footnote:

a. Adverse Events: AEs are reported from the time the subject restarts study drug 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.

b. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration

c. Physical Exam: Vital signs will be collected through end of treatment only. ECOG collected through disease progression.

d. CT Scan: CT scans should be performed prior to reintroduction for restaging, at 4 months, 12 months, and annually thereafter, and as clinically indicated. Please reference Section 7.1.3.2 for details

e. Cytogenetics, FISH panel: Central lab if local FISH lab results are not available or if site cannot perform del17p and del11q testing.

f. IGHV sample will be derived from one of the [redacted] samples collected

g. Karyotype: will be assessed from peripheral blood or bone marrow aspirate samples.

h. Local labs: Hematology, chemistry, Creatinine Clearance, and Coagulation panel may be performed at local labs

Appendix D. Schedule of Assessments for Reintroduction of Venetoclax (MRD Cohort only)

Study Visits	1st month					2nd month	Every 4 months for the first year, then every 6 months until PD (Day 1 of each visit)	Suspected PD (as soon as possible after suspected PD)	Post PD Follow-up (Every 4 months)
	Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
	D-3 or D-2	D-1	D1[a]	D2		D1			
Study Visit Windows	± 3 days (minimum of 7 days at each dose level of venetoclax)						± 3 days	Anytime	±14 d
Study Drug Administration and Dispensation									
venetoclax			**venetoclax:** dose ramp up[b]				**venetoclax:** 400 mg PO daily[b]		
Procedures									
Medical Monitor Approval	Obtained before 1st dose								
Concomitant medications			X		X	X	X	X	
Adverse events[c]			X	X	X	X	X	X	
Study drug compliance review[d]			X		X	X	X	X	
Physical exam, vital signs, weight, ECOG[e]			X		X	X	X	X	
Overall response assessment	X[f]		X				X	X	
CT/MRI scan[f]	X						X at 4 months, 12 months and annually thereafter	X	
Bone marrow biopsy/aspirate for response (local lab and [redacted] central lab)							X (only if suspected CR / to confirm CR)	X (if clinically indicated)	
Tumor Lysis Syndrome (TLS) Risk Assessment[h]	X		X		X	X WK 1			
Tumor Lysis Syndrome Prophylaxis[i]	X	X	X	X	X	X WK1			
Hematology (local lab)[j]	X		X	X	X	X WK1	X	X	
Serum chemistry (local lab)[j]	X		X	X	X	X	X	X	
Creatinine clearance (eg, Cockcroft-Gault) (local lab)			X		X	X			
FISH (local or central lab)[g]			X						
Karyotype (central lab)			X						
IGHV (central lab)[k]			X						
[redacted] assays[k]	[redacted]								

Appendix D. Schedule of Assessments for Reintroduction of Venetoclax (MRD Cohort only) – (Cont.)

Study Visits	1st month					2nd month	Every 4 months for the first year, then every 6 months until PD (Day 1 of each visit)	Suspected PD (as soon as possible after suspected PD)	Post PD Follow-up (Every 4 months)
	Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
	D-3 or D-2	D-1	D1[a]	D2		D1			
Study Visit Windows	± 3 days (minimum of 7 days at each dose level of venetoclax)_						± 3 days	Anytime	±14 d
Survival, including other malignancies									X
Any new anti-cancer therapy									X

Footnote:

a. Day 1: To be collected pre-dose or within +/- 3 days, unless otherwise specified. FISH, Karyotype, IGHV, and [redacted] only on Week 1 D1

b. Venetoclax: Day 1 dose of Cycle 4 Weeks 1-4, and Cycle 5 Week 1 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

c. Adverse Events: AEs are reported from the time the subject restarts study drug 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.

d. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration

e. Physical Exam: Vital signs will be collected through end of treatment only. ECOG collected through disease progression.

f. CT Scan: CT scans should be performed prior to reintroduction for restaging, at 4 months, 12 months, and annually thereafter, and as clinically indicated. C4 CT Scan should be collected at C4D-3, while still allowing for appropriate TLS risk-guided interventions including hospitalizations if appropriate.

g. Cytogenetics, FISH panel: Central lab if local FISH lab results are not available or if site cannot perform del17p and del11q testing.

h. Tumor Lysis Syndrome Risk Assessment: Please see Appendix H for risk assessment categories. For baseline risk assessment, use Screening CT and C1D1 ALC.

i. Tumor Lysis Syndrome Prophylaxis: Please see Section 5.4.2.2 for TLS prophylaxis schedule, venetoclax administration setting and frequency of serum chemistry monitoring assessments.

j. Hematology and Serum Chemistry may be collected up to 24 hours prior to each venetoclax ramp-up (Cycle 4 Weeks 1-4 and Cycle 5 Week 1), to allow for flexibility in start of ramp-up dose. Hematology and serum chemistry can be drawn on day of dosing to allow for comparisons, but results are not required before dosing decision is made. For subjects at high risk for TLS, additional hematology and serum chemistry samples will need to be collected 6-8 and 24 hours post-1st dose at Cycle 4 Weeks 3 and 4 and Cycle 5 Week 1 as part of TLS risk assessment. Please see Table 3 for serum chemistry monitoring assessments.

k. IGHV sample will be derived from one of the [redacted] samples collected
Karyotype: will be assessed from peripheral blood or bone marrow aspirate samples.

Appendix E. Schedule of Assessments for Reintroduction of Ibrutinib + Venetoclax (FD Cohort only)

	1st month – Day 1[a]	4th month					5th month	Every 4 months for the first year, then every 6 months until PD (Day 1 of each visit)	Suspected PD (as soon as possible after suspected PD)	Post PD Follow-up (Every 4 months)
		Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
		D-3 or D-2	D-1	D1	D2		D1			
Study Visit Windows	± 3 days	± 3 days (minimum of 7 days at each dose level of venetoclax)_						± 3 days	Anytime (as soon as possible after suspected PD)	±14 d
Study Drug Administration and Dispensation										
both ibrutinib	**ibrutinib:** 420 mg PO daily									
and venetoclax				**venetoclax:** dose ramp up[b]				**venetoclax:** 400 mg PO daily[b]		
Procedures										
Medical Monitor Approval	Obtained Before 1st Dose									
Concomitant medications	X			X		X	X	X	X	
Adverse events[c]				X	X	X	X	X	X	
Study drug compliance review[d]				X		X	X	X	X	
Physical exam, vital signs, weight, ECOG[e]	X			X		X	X	X	X	
Overall response assessment	X[f]	X						X	X	
CT/MRI scan[f]	X[f]	X						X at 4 months, 12 months, and annually thereafter	X	
Bone marrow biopsy/aspirate for response (local lab and [redacted] central lab)								X (only if suspected CR / to confirm CR)	X (if clinically indicated)	
Tumor Lysis Syndrome (TLS) Risk Assessment[h]		X		X		X	X Wk1			
Tumor Lysis Syndrome Prophylaxis[i]		X	X	X		X	X Wk1			
Hematology (local lab)[j,m]	X	X		X	X	X	X	X	X	
Serum chemistry (local lab)[j,m]	X	X		X	X	X	X	X	X	
Creatinine clearance (eg, Cockcroft-Gault)[m]	X	X		X		X	X			
Coagulation panel[m]	X									
FISH (local or central lab)[g]	X									
Karyotype (central lab)	X									

Appendix E. Schedule of Assessments for Reintroduction of Ibrutinib + Venetoclax (FD Cohort only) – (Cont.)

	1st month – Day 1[a]	4th month					5th month	Every 4 months for the first year, then every 6 months until PD (Day 1 of each visit)	Suspected PD (as soon as possible after suspected PD)	Post PD Follow-up (Every 4 months)
		Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
		D-3 or D-2	D-1	D1	D2		D1			
Study Visit Windows	± 3 days	± 3 days (minimum of 7 days at each dose level of venetoclax)_						± 3 days	Anytime (as soon as possible after suspected PD)	±14 d
IGHV (central lab)[k]	X									
[redacted] Assays[k]	[redacted]									
Survival, including other										X
Any new anti-cancer therapy										X

Footnote:

a. Day 1: To be collected pre-dose or within +/- 3 days, unless otherwise specified

b. Venetoclax: Day 1 dose of Cycle 4 Weeks 1-4, and Cycle 5 Week 1 should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

c. Adverse Events: AEs are reported from the time the subject restarts study drug 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.

d. Study Drug Compliance: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration

e. Physical Exam: Vital signs will be collected through end of treatment only. ECOG collected through disease progression.

f. CT Scan: CT scans should be performed prior to reintroduction for restaging, at 4 months, 12 months, and annually thereafter, and as clinically indicated. C4 CT Scan should be collected at C4D-3, while still allowing for appropriate TLS risk-guided interventions including hospitalizations if appropriate.

g. Cytogenetics, FISH panel: Central lab if local FISH lab results are not available or if site cannot perform del17p and del11q testing.

h. Tumor Lysis Syndrome Risk Assessment: Please see Appendix H for risk assessment categories. For baseline risk assessment, use Screening CT and C1D1 ALC.

i. Tumor Lysis Syndrome Prophylaxis: Please see Section 5.4.2.2 for TLS prophylaxis schedule, venetoclax administration setting and frequency of serum chemistry monitoring assessments.

j. Hematology and Serum Chemistry may be collected up to 24 hours prior to each venetoclax ramp-up (Cycle 4 Weeks 1-4 and Cycle 5 Week 1), to allow for flexibility in start of ramp-up dose. Hematology and serum chemistry can be drawn on day of dosing to allow for comparisons, but results are not required before dosing decision is made. For subjects at high risk for TLS, additional hematology and serum chemistry samples will need to be collected 6-8 and 24 hours post-1st dose at Cycle 4 Weeks 3 and 4, and Cycle 5 Week 1 as part of TLS risk assessment. Please see Table 3 for serum chemistry monitoring assessments.

k. IGHV sample will be derived from one of the [redacted] samples collected
l. Karyotype: will be assessed from peripheral blood or bone marrow aspirate samples.
m. Local labs: Hematology, chemistry, Creatinine Clearance, and Coagulation panel may be performed at local labs

Appendix F. 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, Creech RH, Tormey DC, et al: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed June 6, 2008.

Appendix G. Sample List of Cautionary Medications

Cautionary medications are defined as follows. Refer to Section 6.2.1.1 and 6.2.1.2 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib and venetoclax, respectively.

The below medications apply to both ibrutinib and venetoclax unless otherwise specified.

INHIBITORS OR INDUCERS		SUBSTRATES
Strong CYP3A inhibitors:	**Strong CYP3A inducers:**	**Substrates of P-gp**
boceprevir	Avasimibe	aliskiren
clarithromycin	Carbamazepine	ambrisentan
cobicistat	Phenobarbital	colchicines
conivaptan	Phenytoin	dabigatran etexilate
indinavir	Rifabutin	digoxin
itraconazole	Rifampin	everolimus
ketoconazole	St. John's Wort	fexofenadine
lopinavir		lapatinib
mibefradil		loperamide
nefazodone	**Moderate CYP3A inducers:**	maraviroc
nelfinavir	Bosentan	nilotinib
posaconazole	Efavirenz	ranolazine
ritonavir	Etravirine	saxagliptin
saquinavir	Modafinil	sirolimus
telaprevir	Nafcillin	sitagliptin
telithromycin	Oxcarbazepine	talinolol
troleandomycin	Troglitazone	tolvaptan
voriconazole*		topotecan
Moderate CYP3A inhibitors:	**Weak CYP3A inducers:**	**Substrates of BCRP (Venetoclax only)**
aprepitant	Amprenavir	methotrexate
amprenavir	aprepitant,	mitoxantrone
atazanavir	Armodafinil	irrinotecan
ciprofloxacin	Clobazamechinacea	lapatinib
crizotinib	glucocorticoids (eg, prednisone)	rosuvastatin
darunavir	Nevirapine	sulfasalazine
dronedarone	Pioglitazone	topotecan
erythromycin	Rufinamide	
diltiazem	Vemurafenib	
fluconazole		
fosamprenavir		
imatinib		
isavuconazole		
verapamil		
Weak CYP3A inhibitors:	**Inhibitors of OATP1B1/B3 (Venetoclax)**	**Substrates of OATP1B1/B3 (Venetoclax only)**
alprazolam	gemfibrozil,	atrasentan
amiodarone	Eltrombopag	atorvastatin
amlodipine	Cyclosporine	ezetimibe
atorvastatin	Tipranavir	fluvastatin

INHIBITORS OR INDUCERS		SUBSTRATES
bicalutamide		glyburide
cilostazol		olmesartan
cimetidine	**Inhibitors of BCRP (Venetoclax)**	rosuvastatin
cyclosporine	Cyclosporine	simvastatin acid
fluvoxamine	Geftinib	pitavastatin
fluoxetine		pravastatin
ginkgo		repaglinide
goldenseal	**Inhibitors of P-gp (Venetoclax)**	telmisartan
isoniazid	Amiodarone	valsartan
nilotinib	Azithromycin	
oral contraceptives	Captopril	
pazopanib	Carvedilol	
ranitidine	Cyclosporine	
ranolazine	Dronedarone	
suboxone	Felodipine	
tipranavir/ritonavir	Quercetin	
ticagrelor	Quinidine	
zileuton	Ranolazine	
	Ticagrelor	

* moderate CYP3A inhibitor per ibrutinib human data / clinical studies

Note that this is not an exhaustive list. Further information can be found at the following websites: http://medicine.iupui.edu/clinpharm/ddis/main-table/ and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Appendix H. TLS Risk Category

For the management of tumor lysis syndrome prophylaxis, subjects will be classified in 3 risk categories based on the risk for developing medically concerning TLS with venetoclax administration. The Cycle 3 tumor burden assessed by the nodal disease and absolute lymphocyte count will be used to define each category as described below:

	Low Risk	**Medium Risk**	**High Risk**	
Lymph Nodes	All measurable lymph nodes with the largest diameter <5 cm by radiographic assessment	Presence of any single measurable lymph node with the largest diameter ≥5 cm and <10 cm by radiologic assessment	A single measurable lymph node with the largest diameter ≥5 cm by radiologic assessment.	Any single measurable lymph node with the largest diameter ≥10 cm by radiologic assessment
	AND	**OR**	**AND**	
Absolute Lymphocyte Count	$< 25 \times 10^9$/L	$\geq 25 \times 10^9$/L	$\geq 25 \times 10^9$/L	

Appendix I. Howard Criteria[1] for Laboratory and Clinical TLS

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 μmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr

* In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams perdeciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin, 2007.

[1] Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011; 364:1844-54

Appendix J. Example of Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be notified (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not <50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine.
- Vital signs should be taken at time of all blood draws or any Intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols

In addition to the recommendations in the table below:

- For potassium increase ≥0.5 mmol/L from baseline, or any value >5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine and follow first guideline.
- For phosphorus increase of >0.5 mg/dL AND >4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine.

Abnormality	**Management Recommendations[1,2]**
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine. If further ≥0.2 mmol/L increase in potassium, but still <upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and

Abnormality	Management Recommendations[1,2]
	creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine. o If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notified with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027mmol/L) from pre-dose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine.

Abnormality	Management Recommendations[1,2]
	• If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine.

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals >24 hours after either the first dose or dose escalation (eg, 48 or 72 hours) are as below.

***Note*:** If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

References

1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol.2008;26(16):2767-78.

2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Appendix K. 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.

Appendix L. 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. 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] Platelet counts must be below normal levels to be Grades1 to 4. 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] Hemoglobin levels must be below normal levels to be Grades 1 to 4. 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 M. 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)