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 4.5 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:	**Pre-randomization Phase** Subjects will receive single-agent ibrutinib for 3 cycles (1 cycle = 28 days) followed by ibrutinib + venetoclax combination treatment for at least 12 cycles. ***Primary Objective:*** To determine the minimum residual disease (MRD)-negative clinical response rate of the combination of ibrutinib + venetoclax. ***Secondary Objectives:*** To evaluate: • Safety, tolerability, and determination of the recommended doses for the combination • Overall response rate • Complete response rate • Progression free survival • Hematological improvement • Overall survival • Pharmacokinetics of ibrutinib and venetoclax when dosed in combination **Randomization Phase** Subjects who achieve clinical response and a confirmed MRD-negative clinical response after 12 cycles of the ibrutinib + venetoclax combination will be randomized to continued-ibrutinib (venetoclax discontinued) vs placebo (ibrutinib and venetoclax discontinued). Subjects who do not achieve a confirmed MRD-negative clinical response (MRD-positive) after 12 cycles of the ibrutinib + venetoclax combination will be randomized to continued ibrutinib + venetoclax vs ibrutinib alone (venetoclax discontinued). ***Primary Objective:*** To evaluate if discontinuing ibrutinib, in the setting of a confirmed MRD-negative clinical response with the combination of ibrutinib + venetoclax,

	allows for a treatment holiday as assessed by 1-year disease-free survival. One-year disease-free survival is defined as a continued MRD-negative clinical response without progression or death at least 1 year after randomization. ***Secondary Objectives:*** • MRD-negative clinical response (in MRD-positive randomized subjects) • Safety and tolerability ***Exploratory Objectives:*** • Progression free survival • Overall survival • Outcome of ibrutinib reintroduction after MRD-positive relapse or clinical disease progression (PD) • Identification of potential predictive and/or prognostic, genetic and molecular biomarkers
Study Design:	This is a multicenter, double blind, placebo-controlled, randomized, Phase 2 study of ibrutinib versus placebo after attainment of MRD-negative clinical response with the combination of ibrutinib + venetoclax in subjects with treatment-naïve CLL or SLL. The study consists of a pre-randomization phase (combination treatment phase), a randomization phase, and a post-PD follow-up phase. Please see Section 3.1.1 for full explanation of study design. All subjects who discontinue treatment in the absence of clinical 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. **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 9 cycles (C10D1), 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

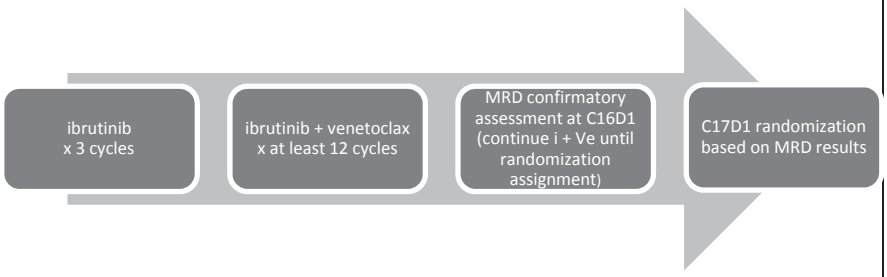
	adjusted accordingly based on this early assessment to adequately power for the Randomization Phase primary endpoint. MRD-negative clinical response for randomization purposes must be confirmed serially over at least 3 cycles and is required to demonstrate negativity in both the bone marrow and peripheral 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. Randomization Phase - MRD-negative subjects (Double-blind): Eligible subjects who achieve a confirmed MRD-negative clinical 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 clinical 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 clinical 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 clinical 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 anytime in subjects who become MRD-negative in PB. Reintroduction of therapy**:** MRD-negative randomized subjects who experience confirmed MRD-positive relapse and/or confirmed clinical disease progression may have their randomization unblinded, and will 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 clinical disease progression by International Worshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, subjects will receive ibrutinib until PD or unacceptable toxicity. Ibrutinib reintroduced subjects who subsequently have confirmed clinical 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 clinical disease progression by IWCLL criteria, subjects can continue ibrutinib and add venetoclax, per standard dose ramp up, until PD or unacceptable toxicity. 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 clinical disease progression by IWCLL criteria, subjects will receive ibrutinib and venetoclax, until PD or unacceptable toxicity. **Post-PD Follow-up Phase:** Subjects who have confirmed clinical disease progression by IWCLL criteria and have discontinued study treatment will be followed for survival status and subsequent anti-cancer therapy until study closure. Assessment of tumor response and progression will be based upon IWCLL criteria (Hallek 2008, Hallek 2012, Hallek 2013, Cheson 2012). The clinical cut-off for primary analysis 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. Based on an estimated enrollment period of 24 months, approximately 16 cycles treatment in pre-randomization phase and 12 cycles treatment in randomization phase for each subject, the total study duration is approximately 52 months from the time the first subject is enrolled 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

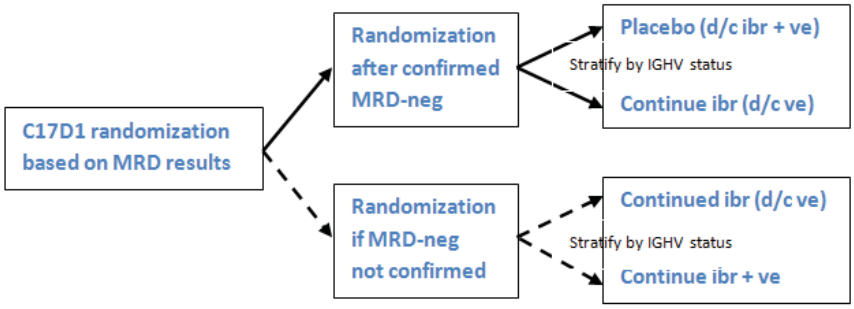
	• Progressive lymphocytosis • Constitutional symptoms 3. Measurable nodal disease by computed tomography (CT). *Laboratory* 4. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screening 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) • Estimated Creatinine Clearance (CrCl) ≥60 mL/min (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 or 1. *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

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

	therapy and 30 days for females 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 for subjects at risk for TLS. 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 C). 18. Currently active, clinically significant hepatic impairment Child-Pugh Class B or C according to the Child Pugh classification (see Appendix G**)**. 19. Lactating or pregnant. 20. Unwilling or unable to participate in all required study evaluations and procedures. 21. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Study Treatment:	**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® USPI, 2016), 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 clinical 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, clinical disease progression or unacceptable toxicity

Randomization Phase – MRD-positive subjects:

Ibrutinib + venetoclax

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

  plus

- Orally once daily venetoclax 400 mg daily (four 100 mg tablets) until clinical disease progression or unacceptable toxicity

OR

Ibrutinib

- Orally once daily ibrutinib 420 mg (3 capsules) continuously until clinical 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 clinical 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 clinical disease progression are confirmed, may reintroduce oral daily ibrutinib (at the last tolerated dose) until clinical disease progression or unacceptable toxicity.

Subjects who are receiving oral daily ibrutinib, when MRD-positive relapse or clinical 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 (VENCLAXTA® USPI, 2016).
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® USPI, 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.
Statistical Methods and Data Analysis:	**Pre-randomization Phase:** *Primary Endpoint:* • Confirmed MRD-negative clinical response rate

	Secondary Endpoints: • Safety, tolerability, and determination of the recommended doses for the combination • Overall response rate • Complete response rate • Progression free survival • Hematological improvement • Overall survival • Pharmacokinetics of ibrutinib and venetoclax when dosed in combination Efficacy and safety analyses will be based on the all-treated population. All endpoints will be summarized descriptively. No inferential tests will be performed. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables. Distribution of PFS and OS will be summarized using the Kaplan-Meier method. Safety endpoints will be summarized descriptively based on subjects who received at least one dose of treatment. **Randomization Phase:** *Primary Endpoint:* • 1-year disease-free rate in MRD-negative randomized subjects *Secondary Endpoint:* • MRD-negative clinical response rate in MRD-positive randomized subjects • Safety and tolerability Exploratory Endpoints: • Progression free survival • Overall survival • Outcome of ibrutinib reintroduction after MRD-positive relapse or PD • Identification of potential predictive and/or prognostic, genetic and molecular biomarkers Efficacy analyses will be based on either MRD-negative randomized subjects or MRD-positive randomized subjects. Safety endpoints will be summarized descriptively based on subjects who received at least one dose of study treatment post randomization.
Sample Size Determination	The study 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 clinical 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 clinical 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 clinical response and to be randomized. The final sample size may be adjusted based on the MRD-negative clinical response rate observed in Pre-randomization Phase.

Appendix A. Schedule of Assessments

Study Visits	Screening Period	Pre-Randomization Phase (1 cycle = 28 days)											Once MRD Status Confirmed Post C16, Proceed to Randomization C17
		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			
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	X												
Physical exam, vital signs, weight, ECOG[g]	X	X	X			X	X	X	X	X	X	X	
Pregnancy	X[r]	X[r]											
Disease assessment[k]:													
CT/MRI scan[i]	X[h]		X[h] C3								X C10	X	
Bone marrow biopsy/aspirate[v]	X[j]												
Overall response assessment[i]				X						X C7	X	X	
Minimal Residual Disease assessment (FACS)[k,v]		X (PB)									X (PB)	X, (BMA & PB)	
Tumor Lysis Syndrome (TLS) Risk Assessment[s]				X		X		X	X Wk1				
Tumor Lysis Syndrome Prophylaxis[t]				X	X	X	X	X	X Wk1				
Hematology[l]	X	X	X	X		X[y]	X	X[y]	X[y]	X	X	X	
Serum chemistry[l]	X	X	X	X		X[y]	X	X[y]	X[y]	X	X	X	
Creatinine clearance (Cockcroft-Gault)[l]	X	X				X		X	X				
Hepatitis serologies[l]	X												
Coagulation panel[l]	X												

Study Visits	Screening Period	Pre-Randomization Phase (1 cycle = 28 days)											
		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	
Study Visit Windows	-30 days	± 3 days								± 3 days			
Procedures (continued)													
Buccal Swab		X											
FISH (central lab)		X[m]											
Karyotype		X (PB)											
IGHV[n]		X											
Biomarker Assays[u]		X	X C3			X[u]				X C7	X	X	
12-lead ECG[o]	X												
Substudies													
PK sample collection[p,q]			X C2							X C6			

Appendix A. Schedule of Assessments - (Cont.)

			Randomization Phase (Including Reintroduction Period)				
			(1 cycle = 28 days)	Suspected MRD-positive	Suspected PD[w]	End-of-Treatment	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	Within 30 Days [z]	Every 3 cycles
Study Visit Windows		within 3 days before C17D1	± 3 days	Any time	Any time	± 3 days	± 14 days
	Study Drug Administration and Dispensation			**Reintroduction**			
MRD-NEG CONFIRMED (Double-Blind)	ibrutinib or		**ibrutinib**: 420 mg PO daily ⇨	Add venetoclax[x]			
	placebo		**placebo**: 3 capsules PO daily ⇨	Add ibrutinib[x]			
MRD-POS CONFIRMED (Open-label)	ibrutinib or		**ibrutinib**: 420 mg PO daily ⇨		Add venetoclax[x]		
	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	
Disease assessment:							
CT/MRI scan[t]			X		X		
Bone marrow biopsy/aspirate [v]					X		
Overall response assessment[i]			X	X	X		
MRD assessment[k]			X (PB,BM)[k]	X (PB)		X (PB)	
Hematology[l]			X	X	X	X	
Serum chemistry[l]			X	X	X	X	
Biomarker Assays[u]			X[v]	X	X	X	
12-lead ECG [o]			If clinically indicated (eg, subjects with palpitations, lightheadedness)				
Survival, including other malignancies							X
Any new anti-cancer therapy							X

Footnote:

a. Cycle 1 D1: To be collected pre-dose, unless otherwise specified

b. Ibrutinib: Day 1 dose of Cycle 1, Cycle 2 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 clinical disease progression. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

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.

i. CT Scan/Overall Response: Overall response assessment by CT Scan will be performed at Cycle 3, Cycle 10, Cycle 16, Cycle 23, Cycle 29, Cycle 35 and then annually thereafter. If study drug is held before a scheduled response assessment then the response assessment can be delayed up to 2 weeks to allow re-initiation of study drug prior to the scheduled response assessment.

j. Bone marrow biopsy and aspirate: should be performed at Screening or up to 90 days before the first dose of study drug and as needed to confirm complete response (CR) or evaluate cytopenia. Bone marrow biopsy collected at Screening will be assessed by local laboratory. An additional bone marrow sample will be sent to central laboratory for karyotype (if ALC ≤ 4000) and future analysis if performed during the screening window. Subjects confirmed as MRD-negative in the marrow/peripheral blood should be followed every 3 cycles for MRD in peripheral blood by flow cytometry.

k. MRD Assessment: should be performed in peripheral blood (PB) at Cycle 1, Cycle 10, 13, 16, 20 and every 3 cycles thereafter. MRD assessment confirmation by both peripheral blood and bone marrow aspirate (BMA) will be performed at Cycle 16 (±14 days). In subjects who consent, an additional BMA can be collected prior to randomization to serially confirm MRD-negativity in the BM compartment. Starting at Cycle 20 and every 3 cycles thereafter MRD assessment by peripheral blood. For all randomized subjects, and any subjects with MRD-neg conversion in PB, an additional BMA should be collected at Cycle 29 (±14 days).

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

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

n. 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.

o. 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.

p. PK (ibrutinib): Day 1 of Cycle 2 and Cycle 6: to be collected pre-dose, 1 hour, 2 hours, 4 hours and 6 hours post-dose.

q. 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.

r. Pregnancy Test: For women of childbearing potential, pregnancy test by serum (at Screeening) and urine (at Cycle 1 Day 1) will be performed.

s. Tumor Lysis Syndrome Risk Assessment: Please see Appendix F for risk assessment categories

t. 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.

u. Biomarker Assays: Collected at Cycles 1, 3, 4 (Week 1 only), 7, 10, 13, 16, 20 and every 3 cycles thereafter.

v. Suspected CR: Collect BM Biopsy, Biomarker assay, and MRD assessment (BMA & PB) at next scheduled study visit.

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

x. 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.

y. 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 24 hours post-1st dose at Weeks 3 and 4 as part of TLS risk assessment. Please see Table 3 for serum chemistry monitoring assessments.

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