APPENDIX 11. SCHEDULE OF ASSESSMENTS (SCREENING AND TREATMENT PERIOD) – ARM A

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm A = 15 treatment cycles														
Cycle	–	–	**C1**	**C2**	**C3**	**C4**				**C5**				**C6**	**C7**	**C10**	**C13**
Day	**-35 to date of enrollment**	**-5 to 0 before C1D1**	**D1[b]**	**D1**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**D1**
Window (day)	–	–	–	**± 3**	**± 3**	–	–	–	–	–	–	–	–	–	**± 3**	**± 7**	**± 7**
Informed consent and screen number[c]	X																
Medical and cancer history and CIRS[d]	X																
Demographic data	X																
IRT enrollment and randomization [e]	X																
Zanubrutinib dispensing and accountability[f]			X	X	X	X				X				X	X	X	X
Sonrotoclax dispensing and accountability[g]						X	X	X	X	X	X	X	X	X	X	X	X
PK sampling (sonrotoclax)[h]														X	X	X	
Safety assessments																	
Vital signs (temperature, BP, and heart rate)[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]	X		X	X	X	X				X				X	X	X	X
Echocardiogram/LVEF	X[k]		X (as clinically indicated)														
ECOG performance status	X		X	X	X	X				X				X	X	X	X
12-Lead ECG (local read)[l] /QTcF	X		X	X	X	X				X				X	X	X	X
TLS risk category determination[m]			X			X											
Concomitant medications review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE review[n]		X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments																	

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm A = 15 treatment cycles														
Cycle	–	–	**C1**	**C2**	**C3**	**C4**				**C5**				**C6**	**C7**	**C10**	**C13**
Day	**-35 to date of enrollment**	**-5 to 0 before C1D1**	**D1[b]**	**D1**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**D1**
Window (day)	–	–	–	**± 3**	**± 3**	–	–	–	–	–	–	–	–	–	**± 3**	**± 7**	**± 7**
Binet staging at screening	X																
Physical examination of liver, spleen, and lymph nodes[p]	X		X			X									X	X	X
Disease-related constitutional symptoms	X		X			X									X	X	X
CT with intravenous and oral contrast[q]/MRI	X					X									X[q]	X	X[q]
Bone marrow biopsy			X[r]														
Disease status/ response assessment[s]	X		X			X									X	X	X
Patient-reported outcomes																	
QLQ-C30			X			X									X	X	X
QLQ-CLL17			X			X									X	X	X
EQ-5D-5L			X			X									X	X	X
PGI-S			X			X									X	X	X
PRO-CTCAE			X			X									X	X	X
Laboratory assessments																	
Hematology[t] and chemistry[u,v]	X		X	X	X	X				X				X	X	X	X
TLS laboratory risk assessment and monitoring[w]						X	X	X	X	X	X	X	X	X			
Serum immunoglobulins[x]	X					X									X	X	X
Coagulation[y]	X																
Coombs test and haptoglobin	X																

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm A = 15 treatment cycles														
Cycle	–	–	**C1**	**C2**	**C3**	**C4**				**C5**				**C6**	**C7**	**C10**	**C13**
Day	**-35 to date of enrollment**	**-5 to 0 before C1D1**	**D1[b]**	**D1**	**D1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**D1**
Window (day)	–	–	–	**± 3**	**± 3**	–	–	–	–	–	–	–	–	–	**± 3**	**± 7**	**± 7**
IGHV mutation analysis[z]	X																
del17p (FISH) and cytogenetics[z]	X																
Complex karyotype[aa]	X																
TP53 mutational analysis[z]	X																
PB and BMA Sample collection for NGS MRD[bb]	X														X		
PB and BMA Sample collection flow cytometry MRD[cc]	X					X									X	X	X
Diagnostic flow cytometry for CLL markers	X																
Resistance mechanism biomarker sample[dd]	X		At unequivocal disease progression														
Hepatitis B, C and HIV testing[ee]	X																
HBV DNA and HCV RNA monitoring by PCR[ff]			Every cycle														
Urinalysis[gg]	X																
Pregnancy test (if applicable)[hh]	X		Every 28 days														

Abbreviations: AE, adverse effect; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; BMA, bone marrow aspirate; BP, blood pressure; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; CT, computed tomography; ECG, electrocardiogram; EQ-5D-5L, Euro QoL 5 dimension 5 level; EORTC, European Organization for Research and Treatment of Cancer; FISH, fluorescence in situ hybridization; GHPS, gated heart pool scan; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HCVAb, hepatitis C antibody; Ig, immunoglobulin; IRT, Interactive Response Technology; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MRD, minimal residual disease; MUGA, multigated acquisition scan; NGS, next-generation sequencing; PB, peripheral blood; PCR, polymerase chain reaction; PGI-S, patient global impression of symptom severity; PK, pharmacokinetic; PRO-CTCAE, National Cancer Institute's Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PTFU, post-treatment follow-up; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-CLL17, Quality of Life

Questionnaire – Chronic Lymphocytic Leukemia Module 17 Items; SAE, serious adverse event; SZ, sonrotoclax plus zanubrutinib; TLS, tumor lysis syndrome; VO, venetoclax plus obinutuzumab.

[a] The time to C1D1 should be within 5 days after randomization/treatment assignment. See Section 7.2.2.

[b] All C1D1 assessments should occur predose unless specified.

[c] This must occur before any study-specific procedures and may be obtained before the 35-day screening window. Consent must be obtained on the current version of the form approved by the ethics committee.

[d] CIRS refers to the cumulative illness rating scale (see Appendix 25).

[e] Patients will be randomized into 1 of 2 arms. Central randomization (1:1) will be used to assign patients to 1 of the following study drug treatments: Arm A (SZ) or Arm B (VO).

[f] Zanubrutinib will be permanently discontinued after Cycle 15. The zanubrutinib drug administration diary will be provided to each patient to record the study drug dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. The complete final patient dosing diary will be provided to the study staff at the completion of treatment on PTFU1 Visit. The patient diary is not applicable during the Post-treatment Follow-up period.

[g] The first dose of sonrotoclax must be administered on C4D1 (no window), however the assessments for C4D1 may be performed within the noted window unless otherwise specified (see footnote w). Sonrotoclax will be permanently discontinued after Cycle 15. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. The complete final patient dosing diary will be provided to the study staff at the completion of treatment on PTFU 1 Visit. The patient diary is not applicable during the Post-treatment Follow-up period. If the ramp-up period is prolonged, delay C6D1 until the first target dose of sonrotoclax is administered. Refer to Section 5.2.1.1.4.

[h] Sparse sonrotoclax PK samples will be collected from approximately 100 patients assigned to Arm A at predose within 30 minutes and at 4 to 6 hours postdose on C6D1, C7D1, and on C10D1. The time of sonrotoclax administration will be recorded.

[i] In addition to the vital signs required for each cycle visit, vital signs will be performed at laboratory collection timepoints for TLS monitoring for the initial sonrotoclax dose and each dose increase.

[j] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at Screening only). The assessment of vital signs and a focused physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days. See Section 7.4.1.

[k] An echocardiogram, MUGA, or GHPS will be performed within 90 days before randomization (ie, a standard of care procedure performed before consent for this study may be used if within window), and as medically necessary.

[l] A 12-lead ECG will be performed in triplicate (≥ 1 minute apart) at screening and at Safety Follow-up Visit. The QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility. During Treatment period visits a single 12-lead ECG read will be performed.

[m] All patients must have an assessment of TLS risk category completed at C1D1 and C4D1 before the first dose of sonrotoclax based on Section 8.1.1. Imaging and hematology laboratory results are required for TLS risk assessment. Risk category must be determined with sufficient time to allow initiation of required TLS medication.

[n] All AEs and SAEs, regardless of relationship to study drug, will be collected and reported until 30 days after the last dose of study drug, the first day of CLL treatment, or until disease progression, whichever occurs earlier. Collect SAE information from the time of signed informed consent through screen failure, until 30 days after the last dose of study drug or until disease progression, whichever occur earlier. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. For all patients, any new second primary malignancy, regardless of severity and relationship to study drug, should be recorded until the end of the study.

[o] AE review must be completed prior randomization.

[p] This procedure can occur at the same time as the physical examination under “Safety Assessment” so long as the visit date adheres to the required visit window for response evaluation.

[q] All patients must have baseline imaging within 35 days before randomization. A CT scan with intravenous and an oral contrast/MRI of the neck, chest, abdomen, pelvis, and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available. Imaging of the neck, chest, abdomen, and pelvis is required for all patients at Screening, C4D1, C10D1, and at the PTFU 1 Visit. NOTE: For C4D1 CT scan/MRI can be performed within 5 days prior to C4D1 visit. Imaging studies will also be performed for confirmation of suspected occurrence of CR or CRi and also promptly at the time of suspected progressive disease based on physical examination findings. Imaging performed outside of the optimal procedure window specified in the Schedule of Assessments will not necessarily be assessed as a protocol deviation; the sponsor will make the final determination. See Section 7.5.3 and Section 7.5.4. Copies of all scans will be sent to the independent review committee for potential response assessment.

[r] A bone marrow biopsy is required at PTFU 1 Visit for patients who have achieved ALC < 4.0 x 10^9/L unless the patient already has obtained bone marrow biopsy that confirmed CR/CRi. After PTFU 1 Visit, a bone marrow core biopsy is required under the following conditions during the Post-treatment Follow-up period starting after PTFU 1 Visit: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy to confirm a CR or CRi if not already confirmed; bone marrow biopsy is required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed; in cases of progression of cytopenia unrelated to autoimmune cytopenia or study treatment, perform a bone marrow biopsy to confirm progressive disease. NOTE: Cytopenic disease progression is documented by a decrease of Hb levels > 2 g/dL or to < 10 g/dL or by a decrease of platelet counts ≥ 50% or to < 100,000/μL, which occurs ≥ 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenia cannot be used to define disease progression. See Section 7.5.5.

[s] Disease status is the baseline assessment of CLL before the first dose of study drug. After the start of study drug: for a timepoint without imaging provide a clinical response evaluation and for a timepoint including imaging provide an overall response evaluation. See Section 7.5.3 and Section 7.5.4.

[t] Complete blood count includes hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1. It is not necessary to duplicate the hematology laboratory tests under “Safety Assessment” and “Efficacy Assessment” so long as the laboratory test results date adheres to the required visit windows for both safety and efficacy assessments.

[u] Serum chemistry will be evaluated by local laboratory and includes sodium, potassium, chloride, bicarbonate or CO2 (or if neither are available, CO2 combining power), glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. NOTE: Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[v] The following 2 chemistry tests will only be done at screening and will be performed locally: direct antiglobulin test and β-2 microglobulin. Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[w] For sonrotoclax ramp-up TLS monitoring: Refer to Appendix 18 timepoints for select serum chemistry (including uric acid, creatinine, phosphorus, potassium and calcium) and complete blood count including hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator. If for logistical reasons, the sonrotoclax dosing must start before the 4-hour predose laboratory results are available for review, an additional set of blood samples must be collected up to 24 hours before sonrotoclax dosing starts. The results from these 24-hour additional predose samples can be used to determine if sonrotoclax dosing may be increased. Additional laboratory assessments may be performed per investigator discretion. The time of sonrotoclax administration at initiation and at each dose increase will be recorded.

[x] Serum immunoglobulin evaluations by local laboratory include IgG, IgM, and IgA.

[y] The coagulation profile includes prothrombin time, which will also be reported as international normalized ratio, and activated partial thromboplastin time. The coagulation profile will be performed at screening only and thereafter as medically indicated by local laboratory.

[z] Prospective baseline biomarker test results for del17p, TP53, and IGHV mutations are required for randomization. A single valid test result by central laboratory for del17p, TP53, and IGHV are needed. All patients will provide peripheral blood samples at the time of screening to assess CLL cytogenetics (eg,

del17p, del11q, and del13q, and to determine Trisomy 12) by FISH and the mutation status of relevant genes such as IGHV, TP53, and other CLL-related prognosis mutations by next-generation sequencing using a specialized central laboratory.

[aa] A peripheral blood sample will be collected during screening to study metaphase karyotype for complex karyotype.

[bb] All patients will have at screening and at C7D1 PB sample submitted for MRD by NGS. All patients will have both PB and BMA samples at PTFU 1 Visit for MRD assessment by NGS method.

[cc] All patients will have screening PB sample submitted for MRD evaluation to establish immunophenotypic profile by a flow cytometry method. All patients must collect both PB and BMA samples at PTFU 1 Visit for MRD assessment by flow cytometry methods. Additionally, serial PB samples will be collected including C4D1, C7D1, C10D1, C13D1 and every 16 weeks from PTFU 1 Visit until unequivocal disease progression. All patients who undergo a bone marrow biopsy for CR or CRi confirmation will also have PB and BMA samples sent to central laboratory for flow cytometry MRD assessment.

[dd] To study the resistance mechanisms of SZ, all patients will be asked to provide a peripheral blood sample at screening, PTFU 1 Visit (Appendix 13), and at the time when unequivocal progressive disease occurs. These peripheral blood samples will be used for exploratory biomarker assessment such as mutation detection and/or molecular profiling to understand potential resistance mechanisms in patients receiving SZ.

[ee] Hepatitis B and C serologies (includes HBsAg, HBsAb, HBcAb and HCVAb) and viral load (HBV DNA will be assessed by polymerase chain reaction (PCR) and HCV RNA by PCR) will be tested at screening as outlined in Section 7.4.4.5. An HIV serology (HIVAb) test will be conducted at screening unless previous HIV test results from ≤ 4 weeks before screening are available. These tests are performed by local laboratory.

[ff] Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo HBV DNA monitoring by PCR at least once on every cycle. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every third cycle. Patients positive for HCV antibody but negative for HCV RNA must have HCV RNA testing every cycle during the study treatment period. After the end of treatment, monitoring of HBV DNA/HCV RNA PCR should continue every 12 weeks for 12 months starting from the last dose of study treatment. See Section 7.4.4.5.

[gg] Urinalysis will include pH, glucose, proteins, ketones, and specific gravity, and a 24-hour urine collection for creatinine clearance test may be performed per investigator's judgement to determine creatinine clearance at screening. Refer to Section 7.4.8.

[hh] All women of childbearing potential (including those who have had a tubal ligation, see Appendix 23) will have a serum pregnancy test ≤ 7 days before the first dose of study drug as part of the screening process. Either serum or urine pregnancy tests will be performed every 4 weeks during the treatment period at specified visits. This will require additional visits after the Cycle 7 Day 1 visit. Either serum or urine pregnancy tests will continue to be performed every 4 weeks until ≥ 90 days after the last dose of study drug in Arm A. This will require additional visits after the Safety Follow-up Visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

APPENDIX 12. SCHEDULE OF ASSESSMENTS (SCREENING AND TREATMENT PERIOD) – ARM B

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm B = 12 treatment cycles										
Cycle	–	–	C1				C2				C3-C6	C7	C10
Day	-35 to date of enrollment	-5 to 0 before C1D1	D1[b]	D8	D15	D22	D1	D8	D15	D22	D1	D1	D1
Window (day)	–	–	–	–	–	–	–	–	–	–	± 3	± 7	± 7
Informed consent and screen number[c]	X												
Medical and cancer history/CIRS[d]	X												
Demographic data	X												
IRT enrollment and randomization[e]	X												
Venetoclax dispensing and accountability[f]						X	X	X	X	X	X	X	X
Obinutuzumab administration			X	X	X		X				X		
Safety assessments													
Vital signs (temperature, BP, and heart rate)[g]	X		X	X	X	X	X	X	X	X	X	X	X
Physical examination[h]	X		X				X				X	X	X
Echocardiogram[i]/LVEF	X		X (as clinically indicated)										
ECOG performance status	X		X				X				X	X	X
12-Lead ECG (local read)[j]/ QTcF	X		X				X				X	X	X
TLS risk category determination[k]			X										
Concomitant medications review	X		X	X	X	X	X	X	X	X	X	X	X
AE review[l]		X[m]	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments													
Binet staging at screening	X												
Physical examination of liver, spleen, and lymph nodes[n]	X		X								C4 only	X	X

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm B = 12 treatment cycles										
Cycle	–	–	C1				C2				C3-C6	C7	C10
Day	-35 to date of enrollment	-5 to 0 before C1D1	D1[b]	D8	D15	D22	D1	D8	D15	D22	D1	D1	D1
Window (day)	–	–	–	–	–	–	–	–	–	–	± 3	± 7	± 7
Disease-related constitutional symptoms	X		X								C4 only	X	X
CT with intravenous and oral contrast[o]/MRI	X										C4 only	X[o]	X
Bone marrow biopsy			X[p]										
Disease status/Response assessment[q]	X		X								C4 only	X	X
Patient-reported outcomes													
QLQ-C30			X								C4 only	X	X
QLQ-CLL17			X								C4 only	X	X
EQ-5D-5L			X								C4 only	X	X
PGI-S			X								C4 only	X	X
PRO-CTCAE			X								C4 only	X	X
Laboratory assessments													
Hematology[r], chemistry[s, t]	X		X				X				X	X	X
TLS laboratory risk assessment and monitoring[u]			X	X	X	X	X	X	X	X			
Serum immunoglobulins[v]	X										C4 only	X	X
Coagulation[w]	X												
Coombs test and haptoglobin	X												
IGHV mutation analysis[x]	X												
del17p (FISH) and cytogenetics[x]	X												
Complex karyotype[y]	X												

	Screening	Enrollment / Randomization[a]	Treatment (1 cycle = 28 days) Arm B = 12 treatment cycles										
Cycle	–	–	C1				C2				C3-C6	C7	C10
Day	-35 to date of enrollment	-5 to 0 before C1D1	D1[b]	D8	D15	D22	D1	D8	D15	D22	D1	D1	D1
Window (day)	–	–	–	–	–	–	–	–	–	–	± 3	± 7	± 7
TP53 mutational analysis[x]	X												
PB and BMA Sample collection for NGS MRD[z]	X												
PB and BMA Sample collection flow cytometry MRD [aa]	X										C4 only	X	X
Diagnostic flow cytometry for CLL markers	X												
Hepatitis B, C and HIV testing[bb]	X												
HBV DNA and HCV RNA monitoring by PCR[cc]			Every cycle										
Urinalysis[dd]	X												
Pregnancy test (if applicable)[ee]	X		Every 28 days										

Abbreviations: AE, adverse event; ALC, absolute lymphocytic count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMA, bone marrow aspirate; BP, blood pressure; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; CT, computed tomography; ECG, electrocardiogram; EQ-5D-5L, Euro QoL 5 dimension 5 level; FISH, fluorescence in situ hybridization; GHPS, gated heart pool scan; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCVAb, hepatitis C antibody; HTLV, human T cell leukemia virus; Ig, immunoglobulin; IV, intravenous; LVEF, left ventricular ejection fraction; MRD, ; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PCR, polymerase chain reaction; PGI-S, patient global impression of symptom severity; PRO-CTCAE, National Cancer Institute's Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PTFU, post-treatment follow-up; QLQ-C30; QLQ-CLL17, Quality of Life Questionnaire – Chronic Lymphocytic Leukemia Module 17 Items; SAE, serious adverse event; TEF, Treatment Eligibility Form; TLS, tumor lysis syndrome; VO, venetoclax plus obinutuzumab.

[a] The time to C1D1 should be within 5 days after randomization/treatment assignment. See Section 7.2.2.

[b] All C1D1 assessments should occur predose unless specified.

[c] This must occur before any study-specific procedures and may be obtained before the 35-day screening window. Consent must be obtained on the current version of the form approved by the ethics committee.

[d] CIRS refers to the cumulative illness rating scale (see Appendix 25).

[e] Patients will be randomized into 1 of 2 arms. Central randomization (1:1) will be used to assign patients to 1 of the following study drug treatments: Arm A (SZ) or Arm B (VO).

[f] Daily as per dosing schedule (20, 50, 100, 200, and 400 mg) for 12 cycles. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. Venetoclax will be administered by mouth once daily

with food, starting with a dose ramp-up period in which 20 mg of venetoclax is given on Cycle 1 Days 22 through 28, 50 mg on Cycle 2 Days 1 through 7, 100 mg on Cycle 2 Days 8 through 14, 200 mg on Cycle 2 Days 15 through 21, and 400 mg from C2D22 onward until C12D28. If the ramp-up period is prolonged, delay C2D22 until the first target dose of venetoclax is administered. See Section 5.2.2.1. The complete final patient dosing diary will be provided to the study staff at the completion of treatment (eg, on or before the Safety Follow-up Visit). The patient diary is not applicable during the Post-treatment Follow-up period.

[g] In addition to the vital signs required for each cycle visit, vital signs will be performed at laboratory collection timepoints for TLS monitoring for the initial venetoclax dose and each dose increase.

[h] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at Screening only). The assessment of vital signs and a focused physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days. See Section 7.4.1.

[i] An echocardiogram, MUGA, or GHPS will be performed within 90 days before enrollment (ie, a standard of care procedure performed before consent for this study may be used if within window), and as medically necessary.

[j] A 12-lead ECG will be performed in triplicate (≥ 1 minute apart) at screening and at Safety Follow-up Visit. The QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility. During Treatment period visits a single 12-lead ECG read will be performed.

[k] All patients must have an assessment of TLS risk category completed at C1D1 before the first dose of obinutuzumab based on Section 8.1.2 and for venetoclax based on Section 8.1.1. Imaging and hematology laboratory results are required for TLS risk assessment. Risk category must be determined with sufficient time to allow initiation of required TLS medication.

[l] All AEs and SAEs, regardless of relationship to study drug, will be collected and reported until 30 days after the last dose of study drug, the first day of CLL treatment, or until disease progression, whichever occurs earlier. Collect SAE information from the time of signed informed consent through screen failure, until 30 days after the last dose of study drug or until disease progression, whichever occur earlier. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. For all patients, any new second primary malignancy, regardless of severity and relationship to study drug, should be recorded until the end of the study.

[m] AE review must be completed before randomization.

[n] This procedure can occur at the same time as the physical examination under “Safety Assessment” so long as the visit date adheres to the required visit window for response evaluation.

[o] All patients must have baseline imaging within 35 days before randomization. A CT scan with intravenous and an oral contrast/MRI of the neck, chest, abdomen, pelvis, and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available. Imaging of the neck, chest, abdomen, and pelvis is **required for all patients at Screening, C4D1, C10D1, and at the PTFU 1 Visit**. Imaging studies will also be performed for confirmation of suspected occurrence of CR or CRi and also promptly at the time of suspected progressive disease based on physical examination findings. Imaging performed outside of the optimal procedure window specified in the Schedule of Assessments will not necessarily be assessed as a protocol deviation; the sponsor will make the final determination. See Section 7.5.3 and Section 7.5.4. Copies of all scans will be sent to the independent review committee for potential response assessment.

[p] A bone marrow biopsy is required at PTFU 1 Visit for patients who have achieved ALC < 4.0 x 10^9/L unless the patient already has obtained bone marrow biopsy that confirmed CR/CRi. After PTFU 1 Visit, a bone marrow core biopsy is required under the following conditions during the Post-treatment Follow-up period starting after PTFU 1 Visit: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy to confirm a CR or CRi if not already confirmed; bone marrow biopsy is required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed; in cases of progression of cytopenia unrelated to autoimmune cytopenia or study treatment, perform a bone marrow biopsy to confirm progressive disease. NOTE: Cytopenic disease progression is documented by a decrease of Hb levels > 2 g/dL or to < 10 g/dL or by a decrease of platelet counts ≥ 50% or to < 100,000/µL, which occurs ≥ 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenia cannot be used to define disease progression. See Section 7.5.5.

[q] Disease status is the baseline assessment of CLL before the first dose of study drug. After the start of study drug: for a timepoint without imaging provide a clinical response evaluation and for a timepoint including imaging provide an overall response evaluation. See Section 7.5.3 and Section 7.5.4.

[r] Complete blood count and differential will be evaluated by a local laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1. It is not necessary to duplicate the hematology laboratory tests under "Safety Assessment" and "Efficacy Assessment" so long as the laboratory test results date adheres to the required visit windows for both safety and efficacy assessments.

[s] Serum chemistry will be evaluated by a local laboratory and includes sodium, potassium, chloride, bicarbonate or CO_2 (or if neither are available, CO_2 combining power), glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. NOTE: Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[t] The following 2 chemistry tests will only be done at screening and will be performed locally: direct antiglobulin test and β-2 microglobulin. Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[u] For obinutuzumab administration during the first cycle (Days 1, 2, 8, and 15) see Section 8.1.2 for TLS monitoring.

For venetoclax ramp-up TLS monitoring: Refer to Appendix 19 timepoints for select serum chemistry laboratory analytes (including uric acid, creatinine, phosphorus, potassium and calcium) and complete blood count including hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator. If for logistical reasons, the venetoclax dosing must start before the 4-hour predose laboratory results are available for review, an additional set of blood samples must be collected up to 24 hours before venetoclax dosing starts. The results from these 24-hour additional predose samples can be used to determine if venetoclax dosing may be increased. Additional laboratory assessments may be performed per investigator discretion. The time of venetoclax administration at initiation and at each dose increase will be recorded.

[v] Serum immunoglobulin evaluations by local laboratory include IgG, IgM, and IgA.

[w] The coagulation profile includes prothrombin time, which will also be reported as international normalized ratio, and activated partial thromboplastin time. The coagulation profile will be performed at screening only and thereafter as medically indicated by local laboratory.

[x] Prospective baseline biomarker test results for del17p, *TP53*, and IGHV mutations are required for randomization. A single valid test result by central laboratory for del17p, *TP53*, and IGHV are needed. All patients will provide peripheral blood samples at the time of screening to assess CLL cytogenetics (eg, del17p, del11q, and del13q, and to determine Trisomy 12) by FISH and the mutation status of relevant genes such as IGHV, *TP53*, and other CLL-related prognosis mutations by next-generation sequencing using a specialized central laboratory.

[y] A peripheral blood sample will be collected during screening to study the metaphase karyotype for complex karyotype.

[z] All patients will have at screening PB sample submitted for MRD by NGS. All patients will have both PB and BMA samples at PTFU 1 Visit for MRD assessment by NGS method.

[aa] All patients will have screening PB sample submitted for MRD evaluation to establish immunophenotypic profile by a flow cytometry method. All patients must collect both PB and BMA samples at PTFU 1 Visit for MRD assessment by flow cytometry methods. Additionally, serial PB samples will be collected including C4D1, C7D1, C10D1, Safety Follow-up Visit and every 16 weeks after PTFU 1 Visit until unequivocal disease progression. All patients who undergo a bone marrow biopsy for CR or CRi confirmation will also have PB and BMA samples sent to central laboratory for flow cytometry MRD assessment.

[bb] Hepatitis B and C serologies (includes HBsAg, HBsAb, HBcAb and HCVAb) and viral load (HBV DNA will be assessed by polymerase chain reaction (PCR) and HCV RNA by PCR) will be tested at screening as outlined in Section 7.4.4.5. An HIV serology (HIVAb) test will be conducted at screening unless previous HIV test results from ≤ 4 weeks before screening are available. These tests are performed by local laboratory.

[cc] Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo HBV DNA monitoring by PCR at least once on every cycle. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every third cycle. Patients positive for HCV antibody but negative for HCV RNA must have HCV RNA testing every cycle during the study treatment period. After the end of treatment, monitoring of HBV DNA/HCV RNA PCR should continue every 12 weeks for 12 months starting from the last dose of study treatment. See Section 7.4.4.5.

[dd] Urinalysis will include pH, glucose, proteins, ketones, and specific gravity, and a 24-hour urine collection for creatinine clearance test may be performed per investigator's judgement to determine creatinine clearance at screening. Refer to Section 7.4.8

[ee] All women of childbearing potential (including those who have had a tubal ligation, see Appendix 23) will have a serum pregnancy test ≤ 7 days before the first dose of study drug as part of the screening process. Either serum or urine pregnancy tests will be performed every 4 weeks during the treatment period at specified visits. This will require additional visits after the Cycle 7 Day 1 visit. Either serum or urine pregnancy tests will continue to be performed every 4 weeks until ≥ 18 months after the last dose of study drug in Arm B. This will require additional visits after the Safety Follow-up Visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

APPENDIX 13. SCHEDULE OF ASSESSMENTS (POST-TREATMENT AND SURVIVAL FOLLOW-UP) – ARM A

Study Period or Visit **Visit**	**Safety Follow-up Visit[a] from the last dose of study drug (after 30 days)**	**Post-treatment Follow-up Period[b]**		**Survival Follow-up Period[c]**
		PTFU 1	**Every 16 weeks beginning from PTFU 2 (PTFU 2, 3, etc)**	**Every 16 weeks**
Day	**–**	**1**	**1**	**1**
Window (Days)	**+ 7**	**+ 14**	**± 14**	**± 14**
Vital signs (temperature, BP, and heart rate)[d]	X			
Physical examination[e]	X			
ECOG performance status	X			
12-Lead ECG (local read)[f] /QTcF	X			
AE review[g]	X	X	X	
Zanubrutinib accountability[h]		X		
Sonrotoclax accountability[i]		X		
PRO questionnaires[j]	X	X	X	
Efficacy Assessments				
Disease-related constitutional symptoms		X	X	
Physical examination of liver, spleen, and lymph nodes[k]		X	X	
CT with intravenous contrast / MRI[l]		X	X[l]	
Bone marrow biopsy[m]		X	X[m]	
Response assessment[n]		X	X	
Survival status data collection[o]				X

Study Period or Visit Visit	Safety Follow-up Visit[a] from the last dose of study drug (after 30 days)	Post-treatment Follow-up Period[b]		Survival Follow-up Period[c]
		PTFU 1	Every 16 weeks beginning from PTFU 2 (PTFU 2, 3, etc)	Every 16 weeks
Day	–	1	1	1
Window (Days)	+ 7	+ 14	± 14	± 14
Laboratory Assessments				
Hematology[p] and chemistry[q,r]	X	X	X	
Serum immunoglobulin[s]		X		
PB and BMA Sample collection for NGS MRD[t]		X		
PB and BMA Sample collection flow cytometry MRD [u]		X	X	
Resistance mechanism biomarker sample[v]	PTFU 1 Visit and at unequivocal disease progression			
HBV DNA and HCV RNA monitoring by PCR (if applicable)[w]	Every 12 weeks			
Pregnancy test (if applicable)[x]	Every 28 days			

Abbreviations: AE, adverse event; ALC, absolute lymphocytic count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMA, bone marrow aspirate; BP, blood pressure; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PB, peripheral blood; PRO, patient-reported outcome; PTFU, post-treatment follow-up; QOL, quality of life; SAE, serious adverse event; SZ, sonrotoclax plus zanubrutinib.

[a] Approximately 30 days after permanent treatment discontinuation or before initiation of a new anticancer therapy, whichever comes first. See Section 3.4 and Section 7.12.

[b] Patients with no assessed unequivocal disease progression at permanent treatment discontinuation will enter Post-Treatment Follow-up period the day after the last dose of study drug. The first Post-Treatment Follow-up (PTFU 1) visit will be performed the day after the last dose of study drug. Subsequent PTFU visits (eg, PTFU 2, PTFU 3) will be performed every 16 weeks always calculated starting from the day after the last dose of study drug and not based on the date of the most recent prior visit. Patients remain on PTFU period until unequivocal disease progression has been assessed. See Section 7.13 for details.

[c] Patients with assessed unequivocal disease progression will enter the Survival Follow-up period until death, withdrawal of patient consent or study closure whichever comes first. Survival Follow-up visits will be performed every 16 weeks based on the day after the last dose of study drug (whichever is latest).

[d] In addition to the vital signs required for each cycle visit, vital signs will be performed at laboratory collection timepoints for TLS monitoring for the initial sonrotoclax dose and each dose increase.

[e] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height needed once at any predose timepoint).

[f] A 12-lead ECG will be performed in triplicate (≥ 1 minute apart) at screening and at Safety Follow-up Visit. The QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility. During Treatment period visits a single 12-lead ECG read will be performed.

[g] All AEs and SAEs, regardless of relationship to study drug, will be collected and reported until 30 days after the last dose of study drug, the first day of CLL treatment, or until disease progression, whichever occurs earlier. Collect SAE information from the time of signed informed consent through screen failure, until 30 days after the last dose of study drug or until disease progression, whichever occur earlier. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. For all patients, any new second primary malignancy, regardless of severity and relationship to study drug, should be recorded until the end of the study.

[h] Zanubrutinib will be permanently discontinued after Cycle 15. The zanubrutinib drug administration diary will be provided to each patient to record the study drug dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. The complete final patient dosing diary will be provided to the study staff at the completion of treatment on PTFU 1 Visit. The patient diary is not applicable during the Post-treatment Follow-up phase.

[i] Sonrotoclax will be permanently discontinued after Cycle 15. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. The complete final patient dosing diary will be provided to the study staff at the completion of treatment on PTFU 1 Visit. The patient diary is not applicable during the Post-treatment Follow-up phase.

[j] PROs will be collected before administration of study drug and medical procedures at baseline (first dose date). If feasible, patients must complete QOL questionnaires before performing any other procedures or study drug administration scheduled for that visit.

[k] This procedure can occur at the same time as the physical examination under “Safety Assessment” so long as the visit date adheres to the required visit window for response evaluation.

[l] All patients must have baseline imaging within 35 days before randomization. A CT scan with intravenous and an oral contrast/MRI of the neck, chest, abdomen, pelvis, and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available. Imaging of the neck, chest, abdomen, and pelvis is **required for all patients at Screening, C4D1, C10D1, and at the PTFU 1 Visit**. Imaging studies will also be performed for confirmation of suspected occurrence of CR or CRi and also promptly at the time of suspected progressive disease based on physical examination findings. Imaging performed outside of the optimal procedure window specified in the Schedule of Assessments will not necessarily be assessed as a protocol deviation; the sponsor will make the final determination. See Section 7.5.3 and Section 7.5.4. Copies of all scans will be sent to the independent review committee for potential response assessment.

[m] A bone marrow biopsy is required at the PTFU 1 Visit for patients who have achieved ALC < 4.0 x 10^9/L unless the patient already has obtained bone marrow biopsy that confirmed CR/CRi. After PTFU 1 Visit, a bone marrow core biopsy is required under the following conditions during the Post-treatment Follow-up period starting after PTFU 1 Visit: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy to confirm a CR or CRi if not already confirmed; bone marrow biopsy is required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed; in cases of progression of cytopenia unrelated to autoimmune cytopenia or study treatment, perform a bone marrow biopsy to confirm progressive disease. NOTE: Cytopenic disease progression is documented by a decrease of Hb levels > 2 g/dL or to < 10 g/dL or by a decrease of platelet counts ≥ 50% or to < 100,000/µL, which occurs ≥ 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenia cannot be used to define disease progression. See Section 7.5.5.

[n] For a timepoint without imaging provide a clinical response evaluation and for a timepoint including imaging provide an overall response evaluation. See Section 7.5.3 and Section 7.5.4.

[o] Patients in survival follow-up will be followed for survival. Contact may be a visit in person or via phone (with the patient’s guardian, if applicable). Additionally, during the survival follow-up period, subsequent new anticancer treatment information, including the reason for starting CLL anticancer treatment, name of each medication along with start date and end date, and date of progression after receiving the subsequent new anticancer treatment will be collected, as well as data regarding second primary malignancy and death. See Section 7.14.

[p] Complete blood count and differential will be evaluated by a local laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1. It is not necessary to duplicate the hematology laboratory tests under "Safety Assessment" and "Efficacy Assessment" so long as the laboratory test results date adheres to the required visit windows for both safety and efficacy assessments.

[q] Serum chemistry will be evaluated by a local laboratory and includes sodium, potassium, chloride, bicarbonate or CO_2 (or if neither are available, CO_2 combining power), glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. NOTE: Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[r] The following 2 chemistry tests will only be done at screening and will be performed locally: direct antiglobulin test and β-2 microglobulin. Serum chemistry testing is not required in the Post-treatment Follow-up phase except at the Safety Follow-up Visit.

[s] Serum immunoglobulin evaluations include IgG, IgM, and IgA.

[t] All patients will have at screening and at C7D1, a PB sample submitted for MRD analysis by NGS. All patients will have both PB and BMA samples at PTFU 1 Visit for MRD assessment by NGS method.

[u] All patients will have screening PB sample submitted for MRD evaluation to establish immunophenotypic profile by a flow cytometry method. All patients must collect both PB and BMA samples at the PTFU 1 Visit for MRD assessment by flow cytometry methods. Additionally, serial PB samples will be collected including C4D1, C7D1, C10D1, C13D1 and every 16 weeks from PTFU 1 Visit until unequivocal disease progression. All patients who undergo a bone marrow biopsy for CR or CRi confirmation will also have PB and BMA samples sent to central laboratory for flow cytometry MRD assessment.

[v] To study the resistance mechanisms of SZ, all patients in treatment arm will be asked to provide a peripheral blood sample at screening, the PTFU 1 Visit, and at the time when unequivocal progressive disease occurs. These peripheral blood samples will be used for exploratory biomarker assessment, such as mutation detection and/or molecular profiling, to understand potential resistance mechanisms in patients receiving SZ.

[w] Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo HBV DNA monitoring by PCR at least once on every cycle. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every third cycle. Patients positive for HCV antibody but negative for HCV RNA must have HCV RNA testing every cycle during the study treatment period. After the end of treatment, monitoring of HBV DNA/HCV RNA PCR should continue every 12 weeks for 12 months starting from the last dose of study treatment. See Section 7.4.4.5.

[x] All women of childbearing potential (including those who have had a tubal ligation, see Appendix 23) will have a serum pregnancy test ≤ 7 days before the first dose of study drug as part of the screening process. Either serum or urine pregnancy tests will be performed every 4 weeks during the treatment period at specified visits. This will require additional visits after the Cycle 7 Day 1 visit. Either serum or urine pregnancy tests will continue to be performed every 4 weeks until ≥ 90 days after the last dose of study drug in Arm A. This will require additional visits after the Safety Follow-up Visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

APPENDIX 14. SCHEDULE OF ASSESSMENTS (POST-TREATMENT AND SURVIVAL FOLLOW-UP) – ARM B

Study Period or Visit	**Safety Follow-up Visit[a] from the last dose of study drug (after 30 days)**	**Post-treatment Follow-up Visit[b]**		**Survival Follow-up Period[c]**
Visit		**PTFU 1**	**Every 16 weeks beginning from PTFU 2 (PTFU 2, 3, etc.)**	**Every 16 weeks**
Day	**–**	**1**	**1**	**1**
Window (Days)	**0 to 7**	**+ 14**	**± 14**	**± 14**
Vital signs (temperature, BP, and heart rate)[d]	X	X	X	
Physical examination[e]	X	X	X	
ECOG performance status	X	X	X	
12-Lead ECG (local read)[f] /QTcF	X			
AE review[g]	X	X[g]	X[g]	
Venetoclax accountability[h]	X			
PRO questionnaires[i]	X	X	X	
Efficacy Assessments				
Disease-related constitutional symptoms	X	X	X	
Physical examination of liver, spleen, and lymph nodes[j]	X	X	X	
CT with intravenous contrast[k]/MRI	X[k]	X	X[k]	
Bone marrow biopsy[l]	X[l]	X	X[l]	
Response assessment[m]	X	X	X	
Survival status data collection[n]				X
Laboratory Assessments				
Hematology[o] and chemistry[p,q]	X	X	X	
Serum Immunoglobulin[r]	X	X		
PB and BMA Sample collection for NGS [s]		X		
PB and BMA Sample collection flow cytometry MRD [t]	X	X	X	
HBV DNA and HCV RNA monitoring by PCR (if applicable)[u]	Every 12 weeks			

Study Period or Visit	Safety Follow-up Visit[a] from the last dose of study drug (after 30 days)	Post-treatment Follow-up Visit[b]		Survival Follow-up Period[c]
Visit		PTFU 1	Every 16 weeks beginning from PTFU 2 (PTFU 2, 3, etc.)	Every 16 weeks
Day	–	1	1	1
Window (Days)	0 to 7	+ 14	± 14	± 14
Pregnancy test (if applicable)[v]	Every 28 days			

Abbreviations: AE, adverse event; ALC, absolute lymphocytic count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; BMA, bone marrow aspirate; BP, blood pressure; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery ; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV DNA, hepatitis B virus DNA; HCV RNA, hepatitis C virus RNA; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; IV, intravenous; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PB, peripheral blood; PCR, polymerase chain reaction; PRO, patient-reported outcome; PTFU, post-treatment follow-up; QOL, quality of life; QTcF, corrected QT interval using Fridericia formula; SAE, serious adverse event; TLS, tumor lysis syndrome.

[a] Approximately 30 days after permanent treatment discontinuation or before initiation of a new anticancer therapy, whichever comes first. See Section 3.4 and Section 7.12.

[b] Patients with no assessed unequivocal disease progression at permanent treatment discontinuation will enter Post-Treatment Follow-up period the day after the last dose of study drug. The first Post-Treatment Follow-up (PTFU 1) visit will be performed after 12 weeks from the day after the last dose of study drug. Subsequent PTFU visits (e.g., PTFU 2) will be performed every 16 weeks based on the day after the last dose of study drug. Patients remain on PTFU period until unequivocal disease progression has been assessed. Refer to Section 7.13 for details.

[c] Patients with assessed unequivocal disease progression will enter Survival Follow-up period until death, withdrawal of patient consent or study closure whichever comes first. Survival Follow-up visits will be performed every 16 weeks based on the day after the last dose of study drug.

[d] In addition to the vital signs required for each cycle visit, vital signs will be performed at laboratory collection timepoints for TLS monitoring for the initial venetoclax dose and each dose increase.

[e] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height needed once at any predose timepoint).

[f] A 12-lead ECG will be performed in triplicate (≥ 1 minute apart) at screening and at Safety Follow-up visit. The QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility. During Treatment period visits a single 12-lead ECG read will be performed.

[g] All AEs and SAEs, regardless of relationship to study drug, will be collected and reported until 30 days after the last dose of study drug, the first day of CLL treatment, or until disease progression, whichever occurs earlier. Collect SAE information from the time of signed informed consent through screen failure, until 30 days after the last dose of study drug or until disease progression, whichever occur earlier. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. For all patients, any new second primary malignancy, regardless of severity and relationship to study drug, should be recorded until the end of the study.

[h] Daily as per dosing schedule (20, 50, 100, 200, 400 mg) for 12 cycles. Any missed doses with explanation should be recorded in the diary. The diary should be brought to the clinic for each visit and will be reviewed by the study coordinator on a regular basis. Venetoclax will be administered by mouth once daily with food, starting with a dose ramp-up period in which 20 mg of venetoclax is given on Cycle 1 Days 22 through 28, 50 mg on Cycle 2 Days 1 through 7, 100 mg on Cycle 2 Days 8 through 14, 200 mg on Cycle 2 Days 15 through 21, and 400 mg from Cycle 2 Day 22 onward until C12D28. If the ramp-up period takes longer than 28 days, the entire Cycle 2 up to D28 when the patient has been 7 days on venetoclax dose of 400 mg per day. Refer to Section 5.2.2.1. The

complete final patient dosing diary will be provided to the study staff at the completion of treatment (eg, on or before the Safety Follow-up Visit). The patient diary is not applicable during the Post-treatment Follow-up phase.

[i] PROs will be collected before administration of study drug and medical procedures at baseline (first dose date). If feasible, patients must complete QOL questionnaires before performing any other procedures or study drug administration scheduled for that visit.

[j] This procedure can occur at the same time as the physical examination under "Safety Assessment" so long as the visit date adheres to the required visit window for response evaluation.

[k] All patients must have baseline imaging within 35 days before randomization. A CT scan with intravenous and an oral contrast/MRI of the neck, chest, abdomen, pelvis, and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available. Imaging of the neck, chest, abdomen, and pelvis is **required for all patients at Screening, C4D1, C10D1, and at the PTFU 1 Visit**. Imaging studies will also be performed for confirmation of suspected occurrence of CR or CRi and also promptly at the time of suspected progressive disease based on physical examination findings. Imaging performed outside of the optimal procedure window specified in the Schedule of Assessments will not necessarily be assessed as a protocol deviation; the sponsor will make the final determination. See Section 7.5.3 and Section 7.5.4. Copies of all scans will be sent for potential independent review committee for response assessment.

[l] A bone marrow biopsy is required at PTFU 1 visit for patients who have achieved ALC < 4.0 x 10^9/L unless the patient already has obtained bone marrow biopsy that confirmed CR/CRi. After PTFU 1 visit, a bone marrow core biopsy is required under the following conditions during the Post-treatment Follow-up period starting after PTFU 1 visit: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy to confirm a CR or CRi if not already confirmed; bone marrow biopsy is required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed; in cases of progression of cytopenia unrelated to autoimmune cytopenia or study treatment, perform a bone marrow biopsy to confirm progressive disease. NOTE: Cytopenic disease progression is documented by a decrease of Hb levels > 2 g/dL or to < 10 g/dL or by a decrease of platelet counts ≥ 50% or to < 100,000/μL, which occurs ≥ 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenia cannot be used to define disease progression. See Section 7.5.5.

[m] For a time point without imaging provide a clinical response evaluation and for a time point including imaging provide an overall response evaluation. See Section 7.5.3 and Section 7.5.4.

[n] Patients in survival follow-up will be followed for survival. Contact may be a visit in person or via phone (with the patient's guardian, if applicable). Additionally, during the survival follow-up period, subsequent new anticancer treatment information, including the reason for starting CLL anticancer treatment, name of each medication along with start date and end date, and date of progression after receiving the subsequent new anticancer treatment will be collected, as well as data regarding second primary malignancy and death. See Section 7.14.

[o] Complete blood count includes hemoglobin, hematocrit, platelet count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1. It is not necessary to duplicate the hematology laboratory tests under "Safety Assessment" and "Efficacy Assessment" so long as the laboratory test results date adheres to the required visit windows for both safety and efficacy Assessments. Additional laboratory assessments may be performed per investigator discretion.

[p] Serum chemistry will be evaluated by includes sodium, potassium, chloride, bicarbonate or CO_2 (or if neither are available, CO_2 combining power), glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. NOTE: Serum chemistry testing is not required in the Post-Treatment Follow-up Period except at the Safety Follow-up Visit. Additional laboratory assessments may be performed per investigator discretion.

[q] The following 2 chemistry tests will only be done at screening and will be performed locally: direct antiglobulin test and β-2 microglobulin. Serum chemistry testing is not required in the Post-Treatment Follow-up Period except at the Safety Follow-up Visit.

[r] Serum immunoglobulin evaluations include IgG, IgM, and IgA.

[s] All patients will have at screening PB sample submitted for MRD by NGS. All patients will have both PB and BMA samples at PTFU 1 visit for MRD assessment by NGS method.

[t] All patients will have screening PB sample submitted for MRD evaluation to establish immunophenotypic profile by a flow cytometry method. All patients must collect both PB and BMA samples at PTFU 1 Visit for MRD assessment by flow cytometry methods. Additionally, serial PB samples will be collected including C4D1, C7D1, C10D1, Safety Follow-up visit and every 16 weeks after PTFU 1 Visit until unequivocal disease progression. All patients who undergo a bone marrow biopsy for CR or CRi confirmation will also have PB and BMA samples sent to central laboratory for flow cytometry MRD assessment.

[u] Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo HBV DNA monitoring by PCR at least once on every cycle. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every third cycle. Patients positive for HCV antibody but negative for HCV RNA must have HCV RNA testing every cycle during the study treatment period. After the end of treatment, monitoring of HBV DNA/HCV RNA PCR should continue every 12 weeks for 12 months starting from the last dose of study treatment. See Section 7.4.4.5.

[v] All women of childbearing potential (including those who have had a tubal ligation, see Appendix 23) will have a serum pregnancy test ≤ 7 days before the first dose of study drug as part of the screening process. Either serum or urine pregnancy tests will be performed every 4 weeks during the treatment period at specified visits. This will require additional visits after the Cycle 7 Day 1 visit. Either serum or urine pregnancy tests will continue to be performed every 4 weeks until ≥ 18 months after the last dose of study drug in Arm B. This will require additional visits after the Safety Follow-up Visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

APPENDIX 15. PHARMACOKINETIC SCHEDULES FOR ARM A (SONROTOCLAX PLUS ZANUBRUTINIB)

Day	**Day 1 of C6, C7, and C10**		
Hours [a]	**Predose**	**Postdose**	
Window (minutes)	**≤ 30**	**4-6 hours**	
PK blood sampling	X	X	X

Abbreviations: eCRF, electronic case report form; PK, pharmacokinetic; (X), optional or conditional assessment.
Note: Actual drug dosing and PK sampling times must be documented by the sites and will be captured in the database.
General note: It is important that PK sampling occurs as close as possible to the scheduled time. To achieve this, some of the other assessments scheduled at the same time may need to be initiated before or after the timepoint to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated timepoint. Thus, the sequence at a particular timepoint is: 1) vital sign measurements; 2) PK blood samples; and 3) any other scheduled or unscheduled measurements at that timepoint.
Sampling window. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained outside of the sampling window will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and eCRF. Hour 24 is 24 hours after the previous day's dose.