NCT03336333

CLINICAL RESEARCH PROTOCOL

Protocol Title:	An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Identifier:	BGB-3111-304
Phase:	3
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
Reference Numbers:	United States IND 125326 EudraCT 2017-001551-31
Sponsor Medical Monitor	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol:	28 June 2017
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Protocol Amendment 3:	11 February 2020
Protocol Amendment 4:	10 February 2021

Confidentiality Statement

FINAL PROTOCOL APPROVAL SHEET

An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BeiGene, Ltd. Approval:

[redacted]

10 Feb 2021

Date

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Zanubrutinib (BGB-3111)

Title of Study: An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Protocol Identifier: BGB-3111-304

Phase of Development: 3

Number of Patients: Approximately 710

Study Centers: Approximately 175

Study Objectives:

All efficacy and safety objectives in Cohort 1 (patients without del17p) will compare zanubrutinib (BGB-3111) versus bendamustine plus rituximab.

Primary:

- To compare efficacy between treatment groups in Cohort 1, as measured by progression-free survival determined by independent central review

Secondary:

- To compare efficacy between Arms A and B in Cohort 1, as measured by the following:
  - Overall response rate determined by independent central review and by investigator assessment
  - Overall survival
  - Duration of response determined by independent central review and by investigator assessment
  - Progression-free survival determined by investigator assessment
  - Patient-reported outcomes
- To compare efficacy between Arms A and B in pooled Cohort 1/1a patients from Chinese sites, as measured by the following:
  - Progression-free survival determined by independent central review and by investigator assessment
  - Overall response rate determined by independent central review and by investigator assessment
  - Duration of response determined by independent central review and by investigator assessment
- To evaluate efficacy in Cohort 2 (patients with del17p) for Arm C, as measured by the following:
  - Overall response rate determined by independent central review and investigator

review
    - Progression-free survival determined by independent central review and investigator review
    - Duration of response determined by independent central review and investigator review
- To evaluate efficacy in Cohort 3 (patients with del17p or pathogenic TP53 variant) for Arm D, as measured by the following:
    - Overall response rate determined by investigator review
    - Progression-free survival determined by investigator review
    - Duration of response determined by investigator review
    - Assess undetectable minimal residual disease at $< 10^{-4}$ sensitivity (undetectable MRD4) at various timepoints in Arm D
- To compare safety between the treatment groups in Cohort 1
- To compare safety between the treatment groups in pooled Cohort 1/1a patients from Chinese sites
- To summarize safety in Cohort 2 (Arm C)
- To summarize safety in Cohort 3 (Arm D)
- To evaluate pharmacokinetics of zanubrutinib (Arms A and C)
- To evaluate pharmacokinetics of zanubrutinib and venetoclax (Arm D)

Exploratory:

- To evaluate the following:
    - Progression-free survival 2 (for Arms A, B, and C) determined by investigator assessment
    - Candidate prognostic and predictive biomarkers and biomarkers of relapse
    - Overall survival in pooled Cohort 1/1a patients from Chinese sites
    - Patient-reported outcomes in pooled Cohort 1/1a patients from Chinese sites
    - Overall survival in Cohort 2
    - Patient-reported outcomes in Cohort 2
    - Overall survival in Cohort 3
    - Patient-reported outcomes in Cohort 3
    - Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax in Cohort 3
- To examine the following:
    - Medical resource utilization in Cohort 1/1a
    - Medical resource utilization in Cohort 2
    - Medical resource utilization in Cohort 3

Study Design:

This is an international (approximately 175 sites), Phase 3, open-label, randomized study of zanubrutinib versus bendamustine plus rituximab (B+R) in approximately 710 adult patients aged 18 and above with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). The study includes approximately 450 patients in Cohort 1 and approximately 80 additional patients from Chinese sites in Cohort 1a to support further analysis in the Chinese population. Patients in both Cohort 1 and Cohort 1a should be without del17p as shown by central laboratory fluorescence in situ hybridization (FISH). The study also includes patients with del17p by central laboratory testing: approximately 100 patients in Cohort 2 and approximately 80 patients in Cohort 3. For patients in Cohort 3 with a central FISH test result other than del17p-positive CLL/SLL, those with a local laboratory test result documenting pathogenic TP53 variant may be eligible for enrollment.

Cohort 1a will be opened to enrollment in China when the Cohort 1 sample size has been reached. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached.

Patients assigned to Cohort 1/1a will be randomized to receive either zanubrutinib monotherapy or B+R. Patients assigned to Cohort 2 (Arm C) will receive zanubrutinib monotherapy. Patients assigned to Cohort 3 (Arm D) will receive venetoclax + zanubrutinib. The primary efficacy endpoint is progression-free survival (PFS) in Cohort 1 determined by independent central review. Disease response will be assessed per the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines (Hallek et al, 2008) with modification for treatment-related lymphocytosis (Hallek et al, 2012; Cheson et al, 2012) for patients with CLL, and per Lugano Classification for Non-Hodgkin Lymphoma (NHL; Cheson et al, 2014) – hereafter referred to as "Lugano Classification for NHL" – for patients with SLL. The modification for treatment-related lymphocytosis is important because treatment with Bruton tyrosine kinase (BTK) inhibitors may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. Analyses have shown that lymphocytosis observed with BTK inhibitor treatment has no bearing on treatment outcome (Woyach et al, 2014).

Cohort assignment will be based on the presence or absence of a specific DNA mutation associated with poor clinical outcomes and poor response to standard chemoimmunotherapy: Cohort 1/1a (without del17p), Cohort 2 (with del17p), and Cohort 3 (with del17p or pathogenic TP53 variant). It is expected that approximately 80-90% of patients will have CLL/SLL without del17p (Moreno et al, 2019) and will be assigned to Cohort 1/1a.

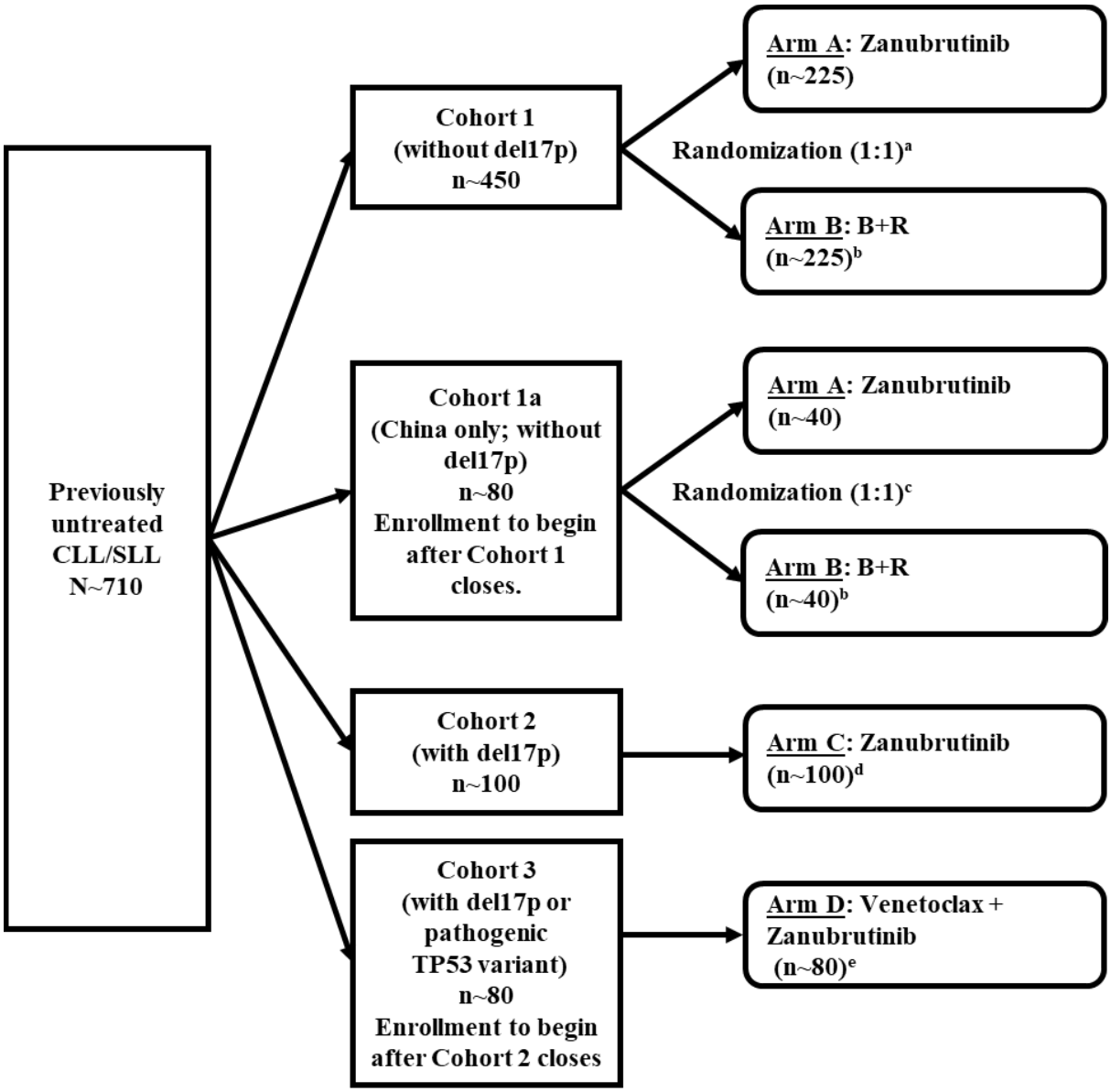
Central randomization (1:1) will be used to assign patients in Cohort 1/1a to one of the following study drug treatments:

- Arm A: zanubrutinib
- Arm B: bendamustine + rituximab (B+R)

Randomization will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), immunoglobulin variable region heavy chain (IGHV) mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific). Because Cohort 1a enrolls only patients from Chinese sites, geographic region will not be a randomization stratification factor for Cohort 1a.

Patients in Cohort 2 (Arm C) will receive treatment with zanubrutinib. Patients in Cohort 3 (Arm D) will receive treatment with venetoclax + zanubrutinib.

Study Schema



Abbreviations: B+R, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma

a. Randomization for Cohort 1 will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific).
b. Crossover for patients in Arm B to receive next-line zanubrutinib is allowed after disease progression is confirmed by independent central review.
c. The same randomization stratification factors used for Cohort 1 will be used for Cohort 1a, except for geographic region.
d. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached.
e. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached.

Treatment with zanubrutinib, treatment with B+R, and treatment with venetoclax + zanubrutinib will be open label. Study treatment should be commenced within 5 days after randomization/treatment assignment. Each cycle consists of approximately 28 days. Study drug treatments will be administered as follows, depending on cohort and treatment assignment:

- Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Arm D only: zanubrutinib will be permanently discontinued in patients who experience unacceptable toxicity, disease progression, or who meet undetectable MRD4 requirements (see Section 6.2.1), unless otherwise agreed by the medical monitor to continue zanubrutinib.
- Bendamustine will be administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles.
- Rituximab will be administered intravenously at a dose of 375 mg/m^2 for Cycle 1, and at a dose of 500 mg/m^2 for Cycles 2 to 6.
- Venetoclax will be administered by mouth once daily with food, starting at Cycle 4 at 20 mg with dose escalation weekly up to 400 mg. Venetoclax will be permanently discontinued in patients who experience unacceptable toxicity, disease progression, or who meet undetectable MRD4 requirements or venetoclax will be continued until 24 cycles of venetoclax are completed, whichever comes first (see Section 6.2.3).

At investigator discretion, patients in Arm B of Cohort 1 may be eligible to receive crossover treatment with zanubrutinib at the time of disease progression confirmed by independent central review. To receive next-line therapy with zanubrutinib, a patient must meet the safety and laboratory requirements documented in Section 5.13, and adhere to the safety, laboratory and efficacy assessments per the zanubrutinib (Arms A and C) Schedule of Assessments (Appendix 10). After crossover, disease response will only be evaluated by the investigator.

Study Assessments:

Assessments of CLL/SLL status to be performed during the study include: disease-related constitutional symptoms; physical examination of lymph nodes, liver, and spleen; complete blood count (CBC); bone marrow examination; genetic alterations in the tumor cells (including del17p, del11q, Trisomy 12, del13q, IGHV mutation analysis); computed tomography (CT) scan of the neck, chest, abdomen, and pelvis; and patient-reported outcomes (PROs; EQ-5D-5L and EORTC QLQ-C30).

All patients (CLL/SLL) must have baseline imaging within 35 days of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and pelvis and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available. For patients who have a contraindication to CT scan with IV contrast at baseline, the following imaging should be performed during Screening and on study in place of CT scan with IV contrast: MRI of the neck, abdomen, and pelvis, and non-contrast CT of the chest. For patients who develop a contraindication to CT scan with IV contrast while on study, see the Radiology Manual for additional details about imaging requirements. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation are kept constant throughout a patient's course on study; additional details can be found in the Radiology Manual. Copies of all scans for patients in Arms A, B, and C will be sent to the independent central review facility for a blinded tumor response assessment. For patients in Arm B who enter crossover, submission of scans for independent central review will be discontinued starting on the day of the first zanubrutinib dose. For patients in Cohort 3 (Arm D), copies of all scans should also be sent to the independent central review facility for potential central assessment.

Imaging of the neck, chest, abdomen, and pelvis by CT with contrast will be performed at Screening and approximately every 12 weeks after the first dose date for 96 weeks (approximately 24 months), then approximately every 24 weeks thereafter, until disease progression (including for patients who

have discontinued or completed study treatment), death, or withdrawal of consent. For patients in Arms A, B, and C, at the time of suspected disease progression, imaging should be provided to the independent central review facility as soon as possible to enable prompt central assessment for disease progression.

Patients in Arms A, B, and C should remain on study treatment (with a maximum of 6 cycles of B+R in Arm B) until unacceptable toxicity or disease progression is confirmed by independent central review. Patients in Arm D should remain on venetoclax until unacceptable toxicity, disease progression, or for a minimum of 12 cycles and a maximum of 24 cycles (based on meeting undetectable MRD4 requirements; see Section 6.2.3). Patients in Arm D should remain on zanubrutinib until unacceptable toxicity, disease progression, or for a minimum of 27 cycles, after which zanubrutinib will be permanently discontinued upon meeting undetectable MRD4 requirements (see Section 6.2.1), unless otherwise agreed with the medical monitor to continue zanubrutinib.

Patients in Arm D will have serial monitoring for undetectable MRD4 status at each scheduled response assessment (see Section 5.10).

To measure potential resistance mechanisms for zanubrutinib, a blood sample will be requested (optional) at time of disease progression from patients receiving zanubrutinib.

Patients with a potential complete response (CR) or complete response with incomplete hematopoietic recovery (CRi) will undergo a bone marrow examination to confirm the CR or CRi, and to determine the presence or absence of minimal residual disease. Assessments of safety will include adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, and vital signs. Nonhematologic AEs will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03; hematological toxicities will be graded based on the Grading Scale for Hematologic Toxicity in CLL Studies (see Appendix 9). For Arm D only, tumor lysis syndrome (TLS) will be graded per the Cairo-Bishop criteria (Appendix 16). An independent Data Monitoring Committee (DMC) will periodically monitor safety data.

Key Eligibility Criteria:

The adult (age ≥ 18 years) patients to be included in this trial will have a confirmed diagnosis of CD20-positive CLL or SLL requiring treatment as defined by at least one of the following: progressive marrow failure; massive, progressive or symptomatic splenomegaly; massive, progressive or symptomatic lymphadenopathy; progressive lymphocytosis with rapid doubling time; autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids; or constitutional symptoms.

Patients must be ≥ 65 years of age at time of informed consent, or < 65 years of age and unsuitable for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) based on 1 or more of the following factors: CIRS score > 6, creatinine clearance < 70 mL/min, or history of previous serious infection and/or multiple infections in the past 2 years (see Section 4.1). Patients will have measurable disease and will have received no prior systemic treatment for CLL/SLL (eligibility allows for 1 prior aborted regimen, see Section 4.2), no history of prolymphocytic leukemia or Richter's transformation, no currently active clinically significant cardiovascular disease, and no active infection including no active hepatitis B or C or HIV. Systemic corticosteroid must be fully tapered off/stopped ≥ 5 days before day of first study drug. Patients in Arm D only: patients who require ongoing treatment with warfarin or warfarin derivatives will be excluded.

Test Product, Dose, and Mode of Administration:

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Arm D only: Patients in Arm D should remain on zanubrutinib until unacceptable toxicity, disease

progression, or for a minimum of 27 cycles, after which zanubrutinib will be permanently discontinued upon meeting undetectable MRD4 requirements (see Section 6.2.1), unless otherwise agreed by the medical monitor to continue zanubrutinib.

Reference Therapy, Dose, and Mode of Administration:

Bendamustine will be administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles.

Rituximab will be administered intravenously at a dose of 375 mg/m^2 for Cycle 1, and at a dose of 500 mg/m^2 for Cycles 2 to 6.

For the first infusion, rituximab should be initiated at a rate of 50 mg/hour. In the absence of infusion toxicity, the infusion rate should increase in 50 mg/hour increments at 30-minute intervals to a maximum of 400 mg/hour. For subsequent infusions, rituximab can be initiated at a rate of 100 mg/hour, and in the absence of infusion toxicity, the infusion rate should increase in 100 mg/hour increments at 30-minute intervals to a maximum of 400 mg/hour. Patients should be premedicated prior to each rituximab infusion with acetaminophen, antihistamine, with or without a glucocorticoid as per institutional standards.

Venetoclax will be administered by mouth once daily with food, starting at Cycle 4 with a dose ramp-up period in which 20 mg of venetoclax is given on Days 1 through 7, 50 mg on Days 8 through 14, 100 mg on Days 15 through 21, 200 mg on Days 22 through 28, and 400 mg from Cycle 5, Day 1 through Cycle 27. Patients in Arm D should remain on venetoclax for a minimum of 12 cycles and a maximum of 24 cycles (based on meeting undetectable MRD4 requirements; see Section 6.2.3).

Statistical Methods:

All inferential statistics described in this section refer to the efficacy comparisons of Arms A and B in Cohort 1. Efficacy results will also be compared for Arms A and B in patients from Chinese sites enrolled in Cohort 1/1a. Separate summary statistics in Cohorts 2 and 3 will be used to report the efficacy and safety of zanubrutinib by each arm. All efficacy analyses in Cohort 1 will be performed using the Intent-to-Treat (ITT) Analysis Set (all patients who are assigned to a treatment group).

Primary Efficacy Endpoint Analysis:

The primary efficacy analysis of progression-free survival will be conducted as assessed by independent central review, using the 2008 iwCLL guidelines with modification for treatment-related lymphocytosis for patients with CLL and using the Lugano NHL 2014 criteria for patients with SLL.

Progression-free survival will be compared between the 2 arms in Cohort 1 using a stratified log-rank test based on the following 3 randomization stratification factors: age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated).

The null and alternative hypotheses for testing progression-free survival superiority of Arm A to Arm B in Cohort 1 are as follows:

H_0: Hazard ratio (HR) (Arm A/Arm B) = 1

H_a: HR (Arm A/Arm B) = 0.58

The HR and its 2-sided 95% confidence interval (CI) will be estimated from a stratified Cox regression model. The distribution of progression-free survival, including median progression-free survival and progression-free survival rate at selected timepoints such as 12 and 24 months, will be estimated using the Kaplan-Meier method for each arm.

There will be 1 interim analysis of progression-free survival by independent central review in Cohort 1, performed when approximately 86 events (73% of the target number of events at final analysis) from Arms A and B are observed. It is estimated that it will take approximately 33 months to observe

86 events. The final analysis of progression-free survival will take place after 118 events are observed in Cohort 1, which is estimated as approximately 41 months from study start.

Secondary Efficacy Endpoint Analysis:

Progression-free survival, overall response rate, and duration of response based on investigator assessment will be analyzed using the same methods employed for the assessment by independent central review.

- Overall response rate (ORR): ORR will be estimated as the crude proportion of patients in each treatment group who achieve PR (including PRL) or higher. Associated 95% Clopper-Pearson CI will be calculated by treatment group. The odds ratio (and 95% CI), which will be provided as a measure of the relative treatment effect, will be estimated using the stratified Cochran-Mantel-Haenszel method.
- Overall survival: Overall survival between the treatment groups will be compared using the same methods employed for the progression-free survival comparison.
- Duration of response: The distribution of duration of response, including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group.
- Patient-reported outcomes: The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be utilized. The scores and their changes from baseline will be summarized and compared between the 2 treatment groups.
- Progression-free survival, ORR, and duration of response for patients from Chinese sites enrolled in Cohort 1/1a will be compared in Arms A and B.

Exploratory Efficacy Endpoint Analyses:

- Progression-free survival 2 for Arms A, B, and C will be compared between the treatment groups using the same methods employed for progression-free survival comparison.
- Cox and/or logistic regression models, as well as descriptive comparisons, may be used to explore the association between prognostic and predictive biomarkers and clinical outcomes.
- Overall survival and patient-reported outcomes for patients from Chinese sites enrolled in Cohort 1/1a will be summarized for Arms A and B.
- Patient-reported outcomes for Cohort 2 will be summarized descriptively.
- Patient-reported outcomes for Cohort 3 will be summarized descriptively.
- Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax for Cohort 3 will be summarized.
- Medical resource utilization will be summarized.

Safety Analysis:

The Safety Analysis Set (all patients who received any dose of study medication) will be used for all safety analyses.

Drug exposure will be summarized by treatment group and study medication, including duration, dosage, and dose intensity.

All treatment-emergent AEs will be summarized. SAEs, deaths, treatment-emergent AEs ≥ Grade 3, study drug-related treatment-emergent AEs, treatment-emergent AEs that led to treatment discontinuation, and dose reductions or dose interruptions will be summarized.

Pharmacokinetic Analysis:

Sparse pharmacokinetic (PK) samples to assess zanubrutinib plasma concentrations will be collected from all patients assigned to Arms A (Cohort 1/1a), C, and D. Optional samples to assess venetoclax plasma concentrations may be collected from patients assigned to Arm D (see Appendix 17). Plasma zanubrutinib and venetoclax concentrations will be summarized by scheduled time of collection. A population PK analysis may be performed to include plasma concentrations from this trial in an existing model. PK parameters such as apparent clearance of the drug from plasma (CL/F) and area under the plasma concentration time curve (AUC) may be derived from the population PK analysis if supported by data.

An exposure-response (efficacy or safety endpoints) analysis may be performed if supported by data. The results from the population PK and exposure-response analyses may be reported separately from the Clinical Study Report (CSR).

Sample Size Considerations:

The sample size calculation for Cohort 1 is based on the primary efficacy analysis of PFS comparison between Arms A and B in Cohort 1. Assuming the HR (Arm A/Arm B) in Cohort 1 is 0.58, 118 events are required to achieve 83.5% power at 2-sided alpha of 0.05 to reject the null hypothesis, when 1 interim analysis is planned after 73% of the target number of events at final analysis. If 450 patients are enrolled to Cohort 1 and randomized in a 1:1 ratio to Arms A and B over a 25-month period (actual patient enrollment up to November 2018 and 28 patients per month enrollment rate after) and the hazard rate for drop-out of 0.0017/month, 118 events are expected to be accumulated at 41 months from study start. This assumes a median PFS in Arm B of 42 months and that PFS follows exponential distribution. Approximately 710 patients will be enrolled, with 450 patients without the del17p mutation in Cohort 1 available for the primary efficacy analysis, approximately 80 additional patients from Chinese sites without the del17p mutation in Cohort 1a, and approximately 100 patients with the del17p mutation in Cohort 2 and approximately 80 patients with del17p or pathogenic TP53 variant in Cohort 3. Sample size selection for Cohort 1a was to accumulate enough PFS events among patients enrolled from Chinese sites at the final analysis to support more than 80% probability of demonstrating an HR < 1 among patients enrolled from Chinese sites if the PFS HR based on the ITT Analysis Set crosses the prespecified statistical boundary at the final analysis. Sample size selections for Cohorts 2 and 3 were driven by estimated patient availability.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
B+R	bendamustine plus rituximab
BGB-3111	zanubrutinib
BTK	Bruton tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CR	complete response
CRi	complete response with incomplete hematopoietic recovery
COVID-19	coronavirus disease
CT	computed tomography
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GHPS	gated heart pool scan
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody

Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
IEC	Independent Ethics Committee
IGHV	immunoglobulin heavy-chain variable region
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat Analysis Set
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MRD	minimum residual disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PFS2	progression-free survival 2
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	partial response
PRL	partial response with lymphocytosis
PRO	patient-reported outcome
SAE	serious adverse event
SD	stable disease
SLL	small lymphocytic lymphoma
TLS	tumor lysis syndrome
ULN	upper limit of normal
Undetectable MRD4	undetectable minimal residual disease at $< 10^{-4}$ sensitivity
WHO	World Health Organization

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) is a malignant disorder of B lymphocytes. It is the most common leukemia in the Western world with an incidence of 4.2 in every 100,000 persons per year. The incidence increases to > 30 in 100,000 per year in people aged more than 80 years. The disease has a median age at diagnosis of 72 years (Eichhorst et al, 2015).

The World Health Organization (WHO) classification considers CLL and small lymphocytic lymphoma (SLL) to be different clinical manifestations of the same disease (Swerdlow et al, 2008); therefore, CLL and SLL are considered collectively. CLL is considered a treatable but essentially incurable disease, and has a heterogeneous course. Therapy is required at the onset of symptomatic disease (either constitutional symptoms or symptoms of worsening lymphadenopathy or organomegaly), clinically significant cytopenias, or rapidly increasing circulating lymphocyte count; these criteria are formalized in the consensus guidance for CLL management (Hallek et al, 2008). Infection is a common complication of the disease, and patients suffering from recurrent infection should receive prophylactic antibiotics and antivirals (Eichhorst et al, 2015). Ultimately, patients who succumb to CLL typically die from infectious complications (due to profound suppression of both cellular and humoral immunity) or, less commonly, from refractory cytopenias. Both can be exacerbated by the cumulative effects of cytotoxic therapy for CLL (Perkins et al, 2002; Griffiths et al, 1992).

In recent decades, the treatment of CLL was based on chemotherapy, particularly the alkylating agents chlorambucil, cyclophosphamide, and more recently, bendamustine. In the 1990s, the purine analogue fludarabine was shown in clinical trials to improve progression-free survival (PFS) compared to chlorambucil, except for elderly CLL patients, and became a standard initial therapy in younger patients with CLL (Rai et al, 2000).

The addition of anti-CD20 antibodies to chemotherapy in the late 1990s resulted in significant improvements in the clinical outcomes of previously untreated CLL (Bauer et al, 2012; Goede et al, 2015; Bryan and Borthakur, 2010). Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes (Reff et al, 1994). Upon binding to CD20, rituximab mediates B-cell lysis, with possible mechanisms of action including complement-dependent cytotoxicity and antibody-dependent cellular toxicity. Circulating CD20-positive B cells are depleted within the first 3 weeks with sustained depletion for up to 6 to 9 months after rituximab treatment in 83% of patients. B-cell recovery begins at approximately 6 months, and median B-cell levels return to normal by 12 months following completion of treatment. The most common adverse events (AEs) associated with rituximab in CLL clinical trials are: infusion reaction, neutropenia, febrile neutropenia, leukopenia, pancytopenia, thrombocytopenia, hypotension, and hepatitis B reactivation. Rituximab is currently approved in the US and Europe for the treatment of CLL.

1.2. Inhibition of B-cell Receptor Signaling

Recently, two new drugs, ibrutinib (Imbruvica®) and idelalisib (Zydelig®) that inhibit the B-cell receptor signaling pathway have shown activity in CLL. Blockade of the B-cell receptor signaling cascade by inhibition of either Bruton tyrosine kinase (BTK; Honigberg et al, 2010) or the delta isoform of phosphoinositide-3-kinase (Zelenetz et al, 2017) causes profound inhibition of proliferative signaling from CLL cell-host interactions, and results in frequent and durable responses in patients with both previously untreated and relapsed/refractory CLL. While the use of phosphoinositide-3-kinase delta inhibitors is often limited by toxicities including hepatotoxicity, colitis, and infectious complications, particularly when used in combination with other agents (Zydelig Summary of Product Characteristics, 2016) and in previously untreated patients (Falchi et al, 2016), the BTK inhibitor ibrutinib has a highly favorable tolerability profile when compared to conventional therapies. Ibrutinib has been shown in randomized trials to significantly improve PFS and overall survival (OS) as compared with the anti-CD20 antibody ofatumumab in relapsed and refractory patients (Byrd et al, 2014) and versus chlorambucil in previously untreated patients (Burger et al, 2015). Both trials demonstrated a significant prolongation of survival, despite allowance of crossover treatment for control arm patients. In April 2016, the Committee for Medicinal Products for Human Use recommended an extension to the approved indications for ibrutinib, and it is now indicated as a single agent for the treatment of adult patients with previously untreated CLL as well as those who have received at least 1 prior therapy (Imbruvica Summary of Product Characteristics, 2016).

1.3. Zanubrutinib

Zanubrutinib is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacologic and toxicologic profile. Zanubrutinib is different from ibrutinib in the following ways:

1. Zanubrutinib is more selective in vitro in the relative inhibition of BTK versus off-target tyrosine kinases, including EGFR, FGR, FRK, HER2, HER4, ITK, JAK 3, LCK, and TEC, which may reduce toxicities possibly due to off-target inhibition such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue;
2. Zanubrutinib has improved oral bioavailability;
3. Zanubrutinib displays significantly less inhibitory effect on rituximab-induced antibody-dependent cell-mediated cytotoxicity, and so is unlikely to adversely impact the antitumor effects of rituximab (Rajasekaran et al, 2014).

1.3.1. Summary of Relevant Nonclinical Data with Zanubrutinib

Summaries of nonclinical studies are provided below. For more detailed information please refer to the current version of the Zanubrutinib (BGB-3111) Investigator's Brochure.

Zanubrutinib is a potent, specific and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nM. Cellular assays confirm that zanubrutinib inhibits B-cell receptor aggregation-triggered BTK autophosphorylation, and blocks downstream PLCγ2 signaling in mantle cell lymphoma cell lines. Zanubrutinib had an IC_{50} of 1.8 nM in a homogeneous time-resolved fluorescence-based BTKpY223 assay. It potently and selectively inhibited cellular growth of several mantle cell lymphoma cell lines (REC-1, Mino and JeKo-1)

and the activated B-cell type diffuse large B-cell lymphoma cell line TMD-8, with IC_{50} values from 0.36 nM to 20 nM, while it was inactive in many other hematologic cancer cell lines.

In vivo studies have demonstrated that zanubrutinib induces dose-dependent antitumor effects against REC-1 mantle cell lymphoma xenografts engrafted either subcutaneously or systemically in mice, which are significantly more effective than ibrutinib. Zanubrutinib also demonstrated better antitumor activity than ibrutinib in TMD-8 diffuse large B-cell lymphoma subcutaneous xenograft model. In a pharmacokinetic (PK)/pharmacodynamic study, oral administration of zanubrutinib resulted in time-dependent occupancy of BTK in blood and in spleen in mice, and was approximately 3-fold more potent than ibrutinib in mouse pharmacodynamic assays.

In a panel of 342 human kinases, 1 μM zanubrutinib inhibited only 12 other kinases by > 70%. Zanubrutinib was more selective than ibrutinib for inhibition of kinase activity of BTK vs EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antibody-dependent cell-mediated cytotoxicity. Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity, consistent with zanubrutinib being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays.

The toxicity profiles of zanubrutinib have been well characterized in rats and dogs. No specific safety concerns were identified in vital organs/systems including cardiovascular system, respiratory system, and central nervous systems. No mortality or severe toxicity was noted in 91-day repeat dose toxicity studies in both rats and dogs at doses up to 300 mg/kg and 100 mg/kg, respectively. Test article-related reversible histopathology changes were mainly noted in rats, including pancreas, spleen, prostate gland, cecum, colon, rectum, skin (lip and/or nose), and uterus. None of the above findings were considered to be adverse in the 91-day repeated dosing studies. No genotoxicity was noted in the genotoxicity core battery studies.

1.3.2. Summary of Relevant Clinical Experience with Zanubrutinib

1.3.2.1. Dose Selection for Zanubrutinib

In the first-in-human, Phase 1 study, BGB-3111-AU-003, the PK of zanubrutinib was linear between 40 mg and 320 mg once a day administered orally. The absorption of zanubrutinib is rapid with median time to maximum plasma concentration (C_{max}) of 2 hours. The terminal elimination half-life is approximately 4 hours at 320 mg once a day. Results from a food effect study showed that zanubrutinib exposure was not altered by high-fat breakfast, and mean area under the plasma concentration time curve (AUC) and C_{max} were increased by 12% and 51%, respectively, with standard breakfast when compared to fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg administered once a day in the ongoing Phase 1 study, and was not associated with any new safety findings; therefore, zanubrutinib can be administered with or without food.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice a day and 320 mg once a day (Tam et al, 2015). At the 160 mg twice a day dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved

in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including CLL, mantle cell lymphoma, Waldenstrom's macroglobulinemia and follicular lymphoma) at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive experience at the 160 mg twice a day and 320 mg once a day dose; both schedules show a high level of activity without compromise of the tolerability profile as compared to lower doses of zanubrutinib. Therefore, the dose of 160 mg administered orally twice a day has been selected as the recommended Phase 3 dose based on sustained target occupancy, high rates of overall response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

1.3.2.2. Clinical Pharmacology

The QT interval prolongation potential of zanubrutinib was evaluated in healthy subjects in a thorough QT study (BGB-3111-106). Results from this study demonstrated that single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including QTc intervals and other ECG intervals. Because of the short half-life and no accumulation seen upon multiple-dosing, these results are also applicable for steady-state conditions.

A dedicated hepatic impairment study (BGB-3111-107) showed that there was no substantial difference in PK between patients with mild/moderate hepatic impairment and healthy subjects. The total and unbound plasma exposures (AUC) of zanubrutinib were 1.60- and 2.9-fold higher in patients with severe hepatic impairment compared to healthy controls.

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg every day for 8 days) decreased exposure of zanubrutinib by 13.5-fold for AUC extrapolated to infinity ($AUC_{0-\infty}$), and 12.6-fold for C_{max}, in healthy subjects. Coadministration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg every day for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. When possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers concomitantly with zanubrutinib and should consider using alternative agents. For cases in which co-administration is needed and used, dose modifications are recommended – see Table 9 (Section 7.3.1).

Additionally, a preliminary physiologically-based pharmacokinetic (PBPK) model was developed and was used to predict the effect of moderate and mild CYP3A inhibitors and CYP3A inducers on the PK of zanubrutinib. PBPK simulations suggest that coadministration of multiple doses of a moderate CYP3A inhibitor (eg, fluconazole, diltiazem, or erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. PBPK simulations suggest that a moderate CYP3A inducer (eg, efavirenz) may decrease the C_{max} and AUC of zanubrutinib by approximately 2 to 3-fold.

A clinical drug-drug interaction study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), and BCRP (rosuvastatin) using a cocktail approach. The results showed that zanubrutinib does not affect drugs metabolized by CYP2C9 (warfarin) or

transported by BCRP (statins). Zanubrutinib had a weak induction effect on CYP3A and CYP2C19 enzymes. AUC from time 0 to the last measurable timepoint (AUC_{0-t}) and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib. Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}.

1.3.2.3. Clinical Efficacy and Safety

For information on the clinical experience for zanubrutinib, please refer to the zanubrutinib (BGB-3111) Investigator's Brochure.

1.4. Benefit-Risk Assessment

As of 08 May 2019, 123 patients with CLL/SLL were enrolled in the Phase 1 BGB-3111-AU-003 study with a median follow-up of 29.5 months (Cull et al 2019). Zanubrutinib was well tolerated, with discontinuation due to AE occurring in only 4% of patients. The overall response rate was 96% and the CR/CRi rate was 16%.

The most frequent AEs of any attribution were contusion (47%, all less than Grade 3), upper respiratory tract infection (42%, all less than Grade 3), diarrhea (31%, Grade 1/2; 1%, Grade 3), cough (29%, all less than Grade 3), headache (24%, all less than Grade 3), and fatigue (19%, Grade 1/2; 1%, Grade 3). One patient had a reported AE that resulted in death (recurrent squamous cell carcinoma).

As of 07 August 2019, 109 patients with previously untreated CLL/SLL harboring the 17p deletion were enrolled into the non-randomized Arm C of this study (BGB-3111-304) (Tam et al, 2019a). With a median follow up of 10.0 months, 63.3% of patients reported no AEs greater than Grade 2 severity. The overall response rate was 92.7% (with 2% CR).

The most frequent adverse events of any attribution were contusion (20%), urinary tract infection (16%), rash (14%), diarrhea (13%), nausea (12%), back pain (11%), and constipation (11%).

Zanubrutinib dose at 160 mg twice a day was chosen over 320 mg daily as the recommended Phase 2 dose due to better 24-hour BTK occupancy (Seymour et al, 2017). These updated results support Phase 3 studies of zanubrutinib in a broad population of CLL/SLL patients.

The initial Phase 2 data for the combination of venetoclax and ibrutinib in patients with treatment-naïve high-risk CLL suggest that the BCL-2 inhibitor plus BTK inhibitor combination is tolerable, with compelling evidence of efficacy (Hillmen et al 2019; Jain et al 2019; Tam et al 2019b). Activity was preserved in patients with the 17p deletion or pathogenic TP53 variant; of note, the tumor suppressor TP53 also lies on chromosome 17p, and somatic pathogenic TP53 mutation has similar effects on risk as deletion (Campo et al 2018; Rafei and Kharfan-Dabaja 2018). The potential for a highly effective and tolerable chemotherapy-free oral regimen for patients with high-risk treatment-naïve CLL is of considerable interest. The availability of finite treatment based on a valid measurement of remission would be a significant benefit for patients. In this protocol, the addition of a treatment arm to study a cohort of patients with del17p-positive or pathogenic TP53 variant-positive CLL/SLL receiving zanubrutinib plus venetoclax is based on these potential benefits.

2. STUDY OBJECTIVES

All efficacy and safety objectives in Cohort 1 (patients without del17p) will compare zanubrutinib versus bendamustine plus rituximab.

Primary:

- To compare efficacy between treatment groups in Cohort 1, as measured by progression-free survival determined by independent central review

Secondary:

- To compare efficacy between Arms A and B in Cohort 1, as measured by the following:
  - Overall response rate determined by independent central review and by investigator assessment
  - Overall survival
  - Duration of response determined by independent central review and by investigator assessment
  - Progression-free survival determined by investigator assessment
  - Patient-reported outcomes
- To compare efficacy between Arms A and B in pooled Cohort 1/1a patients from Chinese sites, as measured by the following:
  - Progression-free survival determined by independent central review and by investigator assessment
  - Overall response rate determined by independent central review and by investigator assessment
  - Duration of response determined by independent central review and by investigator assessment
- To evaluate efficacy in Cohort 2 (patients with del17p) for Arm C, as measured by the following:
  - Overall response rate determined by independent central review and investigator review
  - Progression-free survival determined by independent central review and investigator review
  - Duration of response determined by independent central review and investigator review

- To evaluate efficacy in Cohort 3 (patients with del17p or pathogenic TP53 variant) for Arm D, as measured by the following:
  - Overall response rate determined by investigator review
  - Progression-free survival determined by investigator review
  - Duration of response determined by investigator review
  - Assess undetectable minimal residual disease at $< 10^{-4}$ sensitivity (undetectable MRD4) at various timepoints in Arm D
- To compare safety between the treatment groups in Cohort 1
- To compare safety between the treatment groups in pooled Cohort 1/1a patients from Chinese sites
- To summarize safety in Cohort 2 (Arm C)
- To summarize safety in Cohort 3 (Arm D)
- To evaluate pharmacokinetics of zanubrutinib (Arms A and C)
- To evaluate pharmacokinetics of zanubrutinib and venetoclax (Arm D)

Exploratory:

- To evaluate the following:
  - Progression-free survival 2 (for Arms A, B, and C) determined by investigator assessment
  - Candidate prognostic and predictive biomarkers and biomarkers of relapse
  - Overall survival in pooled Cohort 1/1a patients from Chinese sites
  - Patient-reported outcomes in pooled Cohort 1/1a patients from Chinese sites
  - Overall survival in Cohort 2
  - Patient-reported outcomes in Cohort 2
  - Overall survival in Cohort 3
  - Patient-reported outcomes in Cohort 3
  - Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax in Cohort 3
- To examine the following:
  - Medical resource utilization in Cohort 1/1a
  - Medical resource utilization in Cohort 2
  - Medical resource utilization in Cohort 3

3. STUDY DESIGN

3.1. Summary of Study Design

This is an international (approximately 175 sites), Phase 3, open-label randomized study of zanubrutinib versus bendamustine plus rituximab (B+R) in approximately 710 patients with previously untreated CLL/SLL. The study includes approximately 450 patients in Cohort 1 and approximately 80 additional patients from Chinese sites in Cohort 1a to support further analysis in the Chinese population. Patients in both Cohort 1 and Cohort 1a should be without del17p by central laboratory fluorescence in situ hybridization (FISH). The study also includes patients with del17p by central laboratory testing: approximately 100 patients in Cohort 2 and approximately 80 patients in Cohort 3. For patients in Cohort 3 with a central FISH test result other than del17p-positive CLL/SLL, those with a local laboratory test result documenting pathogenic TP53 variant may be eligible for enrollment.

Cohort 1a will be opened to enrollment in China when the Cohort 1 sample size has been reached. Cohort 2 (Arm C) will receive zanubrutinib monotherapy. Cohort 3 (Arm D) will be opened in selected countries/sites and patients will receive venetoclax + zanubrutinib. Clinical sites in China may continue enrollment into Cohort 1a after the Cohort 1 sample size (approximately 450 patients) has been met in order to meet the China Center for Drug Evaluation (CDE) requirement for approximately 80 additional patients from Chinese sites. Continued enrollment into Cohort 1a will not delay the primary analysis of the study. The primary efficacy endpoint is PFS in Cohort 1 determined by independent central review. Disease response will be assessed per the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines (Hallek et al, 2008) with modification for treatment-related lymphocytosis (Cheson et al, 2012; Appendix 2) for patients with CLL and per Lugano Classification for NHL (Cheson et al, 2014; Appendix 3) for patients with SLL. The modification for treatment-related lymphocytosis is important because treatment with Bruton tyrosine kinase (BTK) inhibitors may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. Analyses have shown that lymphocytosis observed with BTK inhibitor treatment has no bearing on treatment outcome (Woyach et al, 2014).

This study will have the following phases: Screening, Treatment, Post-treatment Follow-up and Long-term Follow-up as described below.

Screening Phase: Screening evaluations will be performed within 35 days before enrollment unless otherwise specified. Patients who agree to participate will sign the informed consent form before any study-specific screening evaluations. Screening procedures are outlined in the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12). Screening evaluations can be repeated.

Treatment Phase: The Treatment phase begins from the time of first dose and continues until the last dose of drug has been taken/received.

Post-treatment Follow-up Phase: The Post-treatment Follow-up phase begins the day after the last dose has been taken and ends at the time of documented disease progression confirmed by independent review committee. NOTE: In Cohort 3 (Arm D) patients, documented disease

progression will be confirmed by investigator assessment; however, the sponsor may additionally choose to confirm disease progression by independent central review.

Long-Term Follow-up Phase: The Long-term Follow-up phase begins the day after documented disease progression confirmed by independent central review (or by investigator assessment for patients in Cohort 3 [Arm D]) and continues until the study ends, or patient death, whichever comes first. NOTE: Patients in Arm B who receive approval for and initiate next-line "crossover" therapy with zanubrutinib will follow the Schedule of Assessments for Arms A and C instead of entering Long-term Follow-up after disease progression (see Section 5.13). Patients who initiate next-line ("crossover") treatment with zanubrutinib will enter Long-term Follow-up at the time of subsequent disease progression per investigator assessment after starting zanubrutinib. Response assessments after crossover will occur per investigator assessment and will not be performed by independent central review.

At the conclusion of the study, patients, who, in the opinion of the investigator, continue to benefit from zanubrutinib at study closure may continue treatment with zanubrutinib either commercially or through a follow-up study.

Cohort assignment will be based on the presence or absence of a specific DNA mutation associated with poor clinical outcomes and poor response to standard chemoimmunotherapy as determined using FISH performed by a central laboratory: Cohort 1 (without del17p), Cohort 2 (with del17p), and Cohort 3 (with del17p, or with a central FISH test result other than del17p-positive CLL/SLL and a local laboratory test result documenting pathogenic TP53 variant). It is expected that approximately 80-90% of patients will not have del17p (Moreno et al, 2019) and will be assigned to Cohort 1/1a.

Central randomization (1:1) will be used to assign patients in Cohort 1/1a to one of the following study drug treatments:

- Arm A: zanubrutinib
- Arm B: bendamustine + rituximab (B+R)

Randomization will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific).

Because Cohort 1a enrolls only patients from Chinese sites, geographic region will not be a randomization stratification factor for Cohort 1a.

Patients in Cohort 2 (Arm C) will receive treatment with zanubrutinib. Patients in Cohort 3 (Arm D) will receive treatment with venetoclax + zanubrutinib.

Treatment with zanubrutinib, with B+R, and with venetoclax + zanubrutinib will be open label. Study treatment should be commenced within 5 days after randomization/treatment assignment. Each cycle consists of 28 days. Study drug treatments will be administered as follows, depending on cohort and treatment assignment:

- Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients in Arms A and C should remain on zanubrutinib until unacceptable toxicity or disease progression. Arm D only: Patients in Arm D should remain on zanubrutinib until unacceptable toxicity, disease progression, or for a minimum of 27 cycles, after which zanubrutinib will be permanently discontinued upon meeting undetectable MRD4 requirements (see Section 6.2.1), unless otherwise agreed by the medical monitor to continue zanubrutinib.
- Bendamustine will be administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles.
- Rituximab will be administered intravenously at a dose of 375 mg/m^2 for Cycle 1 and at a dose of 500 mg/m^2 for Cycles 2 to 6.
- Venetoclax will be administered by mouth once daily with food, starting at Cycle 4 at 20 mg with dose escalation weekly up to 400 mg. Patients in Arm D should remain on venetoclax until unacceptable toxicity, disease progression, or for a minimum of 12 cycles and a maximum of 24 cycles (based upon meeting undetectable MRD4 requirements) (see Section 6.2.3).

At investigator discretion, patients in Arm B of Cohort 1/1a may be eligible to receive crossover treatment with zanubrutinib at the time of disease progression, confirmed by independent central review (Section 5.13). For patients who cross over from Arm B to receive next line zanubrutinib, safety and laboratory assessments will be performed per the zanubrutinib (Arms A and C) Schedule of Assessments (Appendix 10) and tumor response will be evaluated by the investigator.

Study Assessments:

Assessments of CLL/SLL status to be performed during the study include: disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen; complete blood count (CBC); bone marrow examination, genetic alterations in tumor cells (including del17p, del11q, Trisomy 12, del13q, IGHV mutation analysis); computed tomography (CT) scan of the neck, chest, abdomen, and pelvis; and patient-reported outcomes (PROs; EQ-5D-5L and EORTC QLQ-C30). For all study procedures see Section 5, Appendix 10, Appendix 11, and Appendix 12.

All patients (CLL/SLL) must have baseline imaging within 35 days of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and pelvis and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available.

For patients who have a contraindication to CT scan with IV contrast at baseline, the following imaging should be performed during Screening and on study in place of CT scan with IV contrast: magnetic resonance imaging (MRI) of the neck, abdomen, and pelvis, and non-contrast

CT of the chest. For patients who develop a contraindication to CT scan with IV contrast while on study, see the Radiology Manual for additional details about imaging requirements. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation are kept constant throughout a patient's course on study; additional details can be found in the Radiology Manual. Copies of all scans for patients in Arms A, B, and C will be sent to the independent central review facility for a blinded tumor response assessment. For patients in Arm B who enter crossover, submission of scans for independent central review will be discontinued starting on the day of the first zanubrutinib dose. For patients in Cohort 3 (Arm D), copies of all scans should also be sent to the independent central review facility for potential central assessment.

Imaging of the neck, chest, abdomen, and pelvis is required to be performed at Screening and approximately every 12 weeks after the first dose date for 96 weeks (approximately 24 months), then approximately every 24 weeks thereafter, until disease progression (including for patients who have discontinued or completed study treatment), death, or withdrawal of consent. For patients in Arms A, B, and C, at the time of suspected disease progression, imaging should be provided to the independent central review facility as soon as possible to enable prompt central assessment for disease progression.

Pre-treatment bone marrow biopsy slides are required. Bone marrow biopsy and aspirate are required under the following conditions during the Treatment period and Post-treatment Follow-up phase starting at Week 36: if clinical and laboratory results demonstrate a potential CR or CRi, to confirm a CR or CRi (minimal residual disease assessment will also be assessed in the bone marrow and/or blood at this time); if progression of cytopenias is observed unrelated to autoimmune cytopenias or study treatment, to confirm progressive disease. After Week 36, for all study arms, bone marrow core biopsy and aspirate are required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed. For Arms A, B, and C, once CR or CRi in the bone marrow has been confirmed, no further bone marrow biopsy and aspirate are required unless otherwise clinically indicated.

Patients in Arm D will have serial monitoring for undetectable MRD4 status at each scheduled response assessment (see Section 5.10).

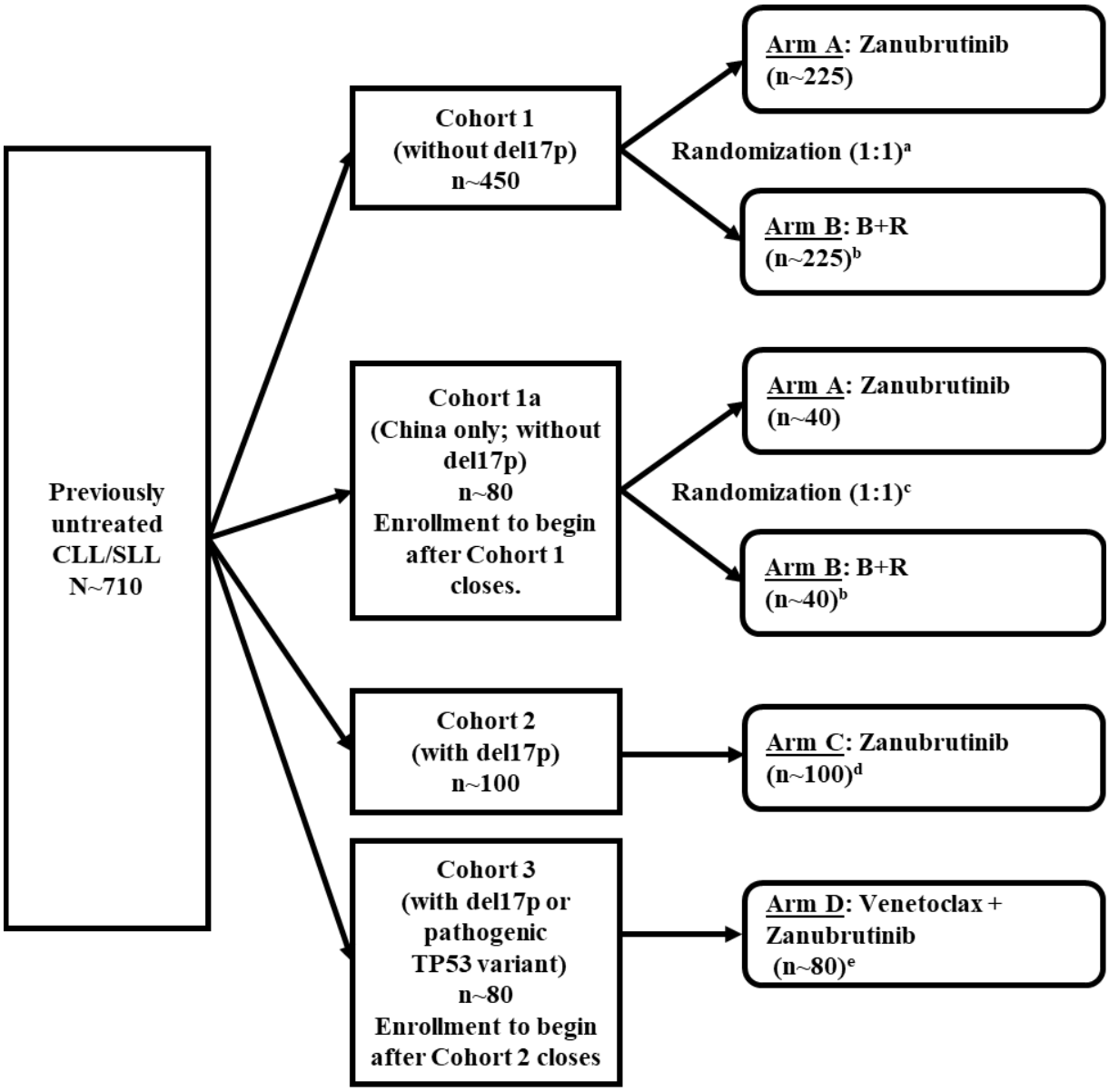
To measure potential resistance mechanisms for zanubrutinib, a blood sample will be requested from patients receiving zanubrutinib who have progressive disease.

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, and vital signs. Nonhematologic AEs will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03; hematological toxicities will be graded based on the Grading Scale for Hematologic Toxicity in CLL Studies (see Appendix 9). For Arm D only, tumor lysis syndrome (TLS) will be graded per the Cairo-Bishop criteria (Appendix 16). An independent Data Monitoring Committee (DMC) will periodically monitor safety data.

3.2. Study Schema

The study schematic is provided in Figure 1.

Figure 1: Study Schema



Abbreviations: B+R, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

a. Randomization for Cohort 1 will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia Pacific).
b. Crossover for patients in Arm B to receive next-line zanubrutinib is allowed after disease progression is confirmed by independent central review.
c. The same randomization stratification factors used for Cohort 1 will be used for Cohort 1a, except for geographic region.
d. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached.
e. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached.

3.3. Blinding

Treatment with zanubrutinib, with B+R, and with venetoclax + zanubrutinib will be open label, however, the assessment of PFS in Cohort 1 by independent central review (primary endpoint) will be blinded.

3.4. Duration of Study

The total duration of this study is expected to be approximately 5 years, assuming an expected enrollment duration of 25 months and a median treatment duration of 42 months after the last enrolled patient in the B+R arm. At the conclusion of the study, patients, who, in the opinion of the investigator, continue to benefit from zanubrutinib at study closure may continue treatment with zanubrutinib either commercially or through a follow-up study.

3.5. Discussion of Study Design, Including Choice of Control Group

This study is designed to test whether treatment with zanubrutinib can prolong PFS as compared with a standard first-line chemoimmunotherapy regimen, B+R, in patients with previously untreated CLL/SLL. Prolongation of PFS is likely to delay or prevent symptoms of progressive CLL/SLL, delay the need for subsequent therapies to treat CLL/SLL, and has been the basis of regulatory approval for several new therapeutic agents, including ibrutinib. The appropriate standard initial treatment regimen for CLL/SLL is dependent upon patient age, presence or absence of comorbidities, and molecular features, particularly the presence of del17p. Infections are a common complication of the disease and of treatment, and the risk of recurrent infection can limit treatment choices. While BTK or phosphoinositide-3-kinase delta inhibitors are considered appropriate for patients with del17p, the standard first-line treatment remains chemoimmunotherapy, and the most commonly used chemoimmunotherapy regimens are B+R and fludarabine, cyclophosphamide, and rituximab (FCR).

The FCR and B+R regimens were compared head-to-head in the German CLL Study Group study, CLL10, in fit patients with previously untreated CLL/SLL without del17p or TP53 mutations (Eichhorst et al, 2016a). The primary analysis of the CLL10 study showed that FCR was superior to B+R in younger males as measured by the primary endpoint of PFS (median PFS was 55.2 months in the FCR group and 41.7 months in the B+R group). For patients aged ≥ 65 years, the outcome was similar for both regimens with less toxicity for B+R. For females, the outcome was similar for both regimens. The FCR regimen was associated with an incidence of severe neutropenia and infection in the 537 patients analyzed in the safety data set, when compared to B+R (84% vs 59% and 39% vs 25%, respectively). Furthermore, at the time of cut-off, 6 patients in the FCR had developed myelodysplasia or secondary acute myelocytic leukemia, as compared with 1 patient in the B+R arm. There was no statistical difference in OS at the time of data cut-off. Given that most patients with CLL/SLL are elderly with comorbidities, the use of the FCR regimen appears limited to the minority subset of patients who are young and fit.

Based on the results of CLL10, the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommend the B+R regimen for fit patients who do not have the del17p or a TP53 mutation as an alternative to FCR for patients with previous history of infections (Eichhorst et al, 2016b; Eichhorst et al, 2015). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for CLL/SLL recommend the B+R regimen as first-line

therapy for CLL/SLL in patients ≥ 65 years, and for younger patients with significant comorbidities (NCCN Treatment Practice Guidelines CLL/SLL, 2017).

The patient population for the primary objective in this study (Cohort 1) of zanubrutinib in CLL/SLL is comparable to the patient population in the CLL10 study, except that this protocol excludes the subset of patients who are young and fit and who should be treated with FCR. In addition, patients with CLL/SLL with del17p will be assigned to Cohort 2 or Cohort 3 because this patient population has poor clinical outcomes and poor response to chemoimmunotherapy. Patients in Cohort 2 (Arm C) will receive single-agent zanubrutinib. Patients in Cohort 3 (Arm D) will receive venetoclax + zanubrutinib.

Cohort 3 (Arm D) will explore the benefits of treatment with combination venetoclax + zanubrutinib. BTK inhibitors have shown remarkable activity in CLL/SLL and ibrutinib is now approved for both previously untreated and previously treated patients. Zanubrutinib has the potential to demonstrate better efficacy and safety than ibrutinib because of higher selectivity of inhibition of BTK versus off-target tyrosine kinases and greater BTK inhibition in lymph nodes and peripheral blood.

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL and AML cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics (VENCLEXTA USPI, Nov 2018; Venclyxto SmPC, May 2018). In nonclinical studies, venetoclax demonstrated cytotoxic activity in tumor cells that overexpress BCL-2. For additional venetoclax nonclinical and clinical background data, refer to the current venetoclax label (VENCLEXTA USPI, Nov 2018; Venclyxto SmPC, May 2018).

Three previous studies of BTK-inhibitor and venetoclax combination therapy, both in the previously untreated and relapsed or refractory settings, have been presented, with results showing tolerability and compelling efficacy (Hillmen et al, 2019; Jain et al, 2019; Tam et al, 2019b). In each, the design of the study included a run-in period with BTK inhibitor alone, followed by combination with venetoclax for up to 1 to 2 years, to reduce the risk of TLS. In Cohort 3 (Arm D), the combination of zanubrutinib and venetoclax will be studied in treatment naïve patients with high risk del17p genomic aberration or pathogenic TP53 variants. Similar to prior studies, patients will receive zanubrutinib for a 3-cycle run-in period, followed by between 12 and 24 cycles of combination therapy with venetoclax. Patients will undergo serial monitoring for undetectable MRD4 at each scheduled response assessment and, if they meet undetectable MRD4 requirements, will permanently discontinue zanubrutinib after receiving 27 cycles (see Section 6.2.1), unless otherwise agreed with the medical monitor to continue zanubrutinib, and may permanently discontinue venetoclax before receiving the full 24 cycles of combination therapy (see Section 6.2.3).

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Patients must be unsuitable for treatment with FCR defined as: ≥ 65 years of age at the time of informed consent, OR 18 - 64 years of age and have one or more of the following factors:

   a. Cumulative Illness Rating Scale (CIRS) score > 6
   b. A CIRS is not required, it may be used to meet this inclusion requirement.
   c. Creatinine clearance < 70 mL/min
   d. History of previous serious infection or multiple infections in the past 2 years

      'Previous serious infection' is defined as infection requiring hospitalization, parenteral antibiotic therapy, or both. 'Multiple infections' is defined as at least 3 infections requiring at minimum oral antibiotic therapy.

   NOTE: Patient preference is not allowed as a reason for "unsuitability for FCR". For Arm D only, central laboratory confirmation of del17p-positive CLL/SLL will fulfill the requirement for unsuitability for FCR. For patients with a central FISH test result other than del17p-positive CLL/SLL, a local laboratory test result documenting pathogenic TP53 variant may meet this requirement (refer to Inclusion Criterion 12).

2. Confirmed diagnosis of CD20-positive CLL or SLL that meets the iwCLL criteria (Hallek et al, 2008)

3. Measurable disease by CT/MRI. Measurable disease is defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters.

4. CLL/SLL requiring treatment based on at least one of the following criteria (Hallek et al, 2008):

   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
   b. Massive (≥ 6 cm below left costal margin), progressive or symptomatic splenomegaly
   c. Massive nodes (≥ 10 cm in longest diameter), or progressive or symptomatic lymphadenopathy
   d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or lymphocyte-doubling time of < 6 months. Lymphocyte-doubling time may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of < 30×10^9/L (30,000/μL), lymphocyte-doubling time should not be used as a single parameter to define treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL/SLL (eg, infection) should be excluded.

e. NOTE: Original subcriterion "e" has been removed. Please see Exclusion Criterion 21.
f. Constitutional symptoms, defined as any 1 or more of the following disease-related symptoms or signs:

i. Unintentional weight loss of ≥ 10% within the previous 6 months

ii. Significant fatigue (ie, inability to work or perform usual activities)

NOTE: Patients with significant fatigue cannot have an ECOG score of 0

i. Fevers > 100.5º F or 38º C for ≥ 2 weeks without other evidence of infection

ii. Night sweats for > 1 month without evidence of infection

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
6. Life expectancy ≥ 6 months
7. Adequate bone marrow function as defined by:
   a. Absolute neutrophil count (ANC) ≥ 1000/mm^3, except for patients with bone marrow involvement in which ANC must be ≥ 750/mm^3
      NOTE: The screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim (or other pegylated myeloid growth factors) and at least 7 days following the most recent administration of filgrastim or other myeloid growth factors
   b. Platelet ≥ 75,000/mm^3, except for patients with bone marrow involvement by CLL in which the platelet count must be ≥ 50,000/mm^3
      NOTE: The screening platelet count may be obtained post-transfusion
8. Patient must have adequate organ function defined as:
   a. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or the Modification of Diet in Renal Disease [MDRD] equation or as measured by nuclear medicine scan or 24-hour urine collection)
   b. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 2.5 × upper limit of normal (ULN) unless due to CLL/SLL
   c. Serum total bilirubin < 3.0 × ULN (unless documented Gilbert's syndrome)
9. Female patients of childbearing potential must practice highly effective methods of contraception (see Section 5.1.2) initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, ≥ 30 days after the last dose of venetoclax, 3 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
10. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception with other methods described above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib or 6 months after the last dose of bendamustine, whichever is longer.
11. Ability to provide written informed consent and can understand and comply with the requirements of the study.

12. Must have FISH results from the study-specified central laboratory confirming the presence or absence of del17p.
    a. For Arm D only: Patients must have a central laboratory FISH test for del17p performed. A patient with a result other than "with del17p" may be eligible only if the patient has a pathogenic TP53 variant previously documented per local laboratory test meeting the criteria specified in Appendix 18. Approval for enrollment by the medical monitor is required.

4.2. Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Previous systemic treatment for CLL/SLL (other than 1 aborted regimen < 2 weeks in duration and > 4 weeks before randomization).
2. Requires ongoing need for corticosteroid treatment. NOTE: Systemic corticosteroids must be fully tapered off/stopped at least 5 days before day of first study drug.
3. Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation
4. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within 6 months before screening
    b. Unstable angina within 3 months before screening
    c. New York Heart Association class III or IV congestive heart failure (see Appendix 4)
    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    e. QTcF > 480 msecs based on Fridericia's formula (NOTE: QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility)
    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening
5. Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
6. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
7. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug
8. Severe or debilitating pulmonary disease

9. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
10. Active fungal, bacterial and/or viral infection requiring systemic therapy
11. Known central nervous system involvement by leukemia or lymphoma
12. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs
13. Known infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (NOTE: the limit of detection for HBV DNA must have a sensitivity of < 20 IU/mL; see Section 5.9), and if they are willing to undergo monitoring every 4 weeks for HBV reactivation.
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
14. Major surgery within 4 weeks of the first dose of study drug
15. Pregnant or lactating women
16. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
17. Ongoing alcohol or drug addiction
18. Hypersensitivity to zanubrutinib, bendamustine, rituximab, or venetoclax (as applicable) or any of the other ingredients of the applicable study drugs
19. Requires ongoing treatment with a strong CYP3A inhibitor or inducer (see Appendix 5)
20. Concurrent participation in another therapeutic clinical trial.
21. Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (eg, idiopathic thrombocytopenia purpura).
22. Arm D only: requires ongoing treatment with warfarin or warfarin derivatives.

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12).

Visit Windows

A study visit may be scheduled on any day within a specified study week. The visit windows are stated in the Schedule of Assessments. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.1. Screening

5.1.1. Informed Consent

At the screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the informed consent form will be given to the patient to read and the patient must have adequate time to digest and ask questions.

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 35-day screening period. Consent must be obtained using the most current version of the form approved by the ethics committee.

Repeating screening procedures or tests is allowed if the patient did not previously meet the inclusion and exclusion criteria or if needed to have a documented result within the protocol-specified screening window.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before randomization, study site personnel should document the screen failure in the patient's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

5.1.2. Females of Childbearing Potential and Contraception

A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Contraception methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation. Patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well.
  - Oral, intravaginal or transdermal

- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, 3 months after the last dose of bendamustine, ≥ 30 days after the last dose of venetoclax, or 12 months after the last dose of rituximab, whichever is longer). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

5.2. Enrollment and Randomization

All study-specific screening procedures must be performed within 35 days before enrollment, unless noted otherwise; assessments not completed within this interval must be repeated. The site investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant. Patient number will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

Medical and Cancer History

Review any medical and cancer history any time after obtaining informed consent; includes presence or absence of disease-related constitutional symptoms. Clinically significant medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the patient's

study eligibility will be collected and captured in the electronic case report form (eCRF). Clinically significant is defined as any events, diagnoses or laboratory values requiring treatment, follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Other background information to be collected includes: history of disease (including the date of initial diagnosis and current disease status), staging, sites of disease, and presence or absence of disease-related constitutional symptoms. Prior medications/significant non-drug therapies and demographic data (gender, date or year of birth [or age] and race/ethnicity) will also be collected.

Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. All patients must have the reason for unsuitability for receiving FCR documented. No eligibility waivers will be granted. After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet and email it to the medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.

Enrollment/Randomization

Access the IRT system to enroll, randomize patient to treatment, and assign study drugs. Study treatment should be commenced within 5 days after randomization/treatment assignment.

5.3. Electrocardiogram

Obtain per local practice and read locally to confirm eligibility. A 12-lead electrocardiogram (ECG) will be performed in triplicate (at least 1 minute apart) at screening. Patients should be in the semi-recumbent or supine position.

5.4. Zanubrutinib Dispensation

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. Instructions are to be provided for dosing, storage, and the return of all bottles (used and unused) at future visits.

5.5. Pharmacokinetics

For patients assigned to Arm A (Cohort 1/1a) and Arm C (zanubrutinib), blood will be collected to characterize the PK of zanubrutinib. For patients assigned to Arm D (zanubrutinib monotherapy run-in and co-administration of zanubrutinib and venetoclax), blood will be collected to characterize the PK of zanubrutinib and venetoclax. Close monitoring of zanubrutinib drug concentrations may be needed by taking additional unscheduled PK samples in the event of suspected drug-drug interactions (eg, when a strong or moderate CYP3A inducer must be used for control of infection).

Pharmacokinetics for Patients Assigned to Arm A and Arm C

Sparse PK samples for zanubrutinib will be collected from all patients assigned to Arm A (Cohort 1/1a) and Arm C (zanubrutinib) at the following timepoints: predose (≤ 30 min prior to morning dose), and 2 hours (± 30 min) postdose for the morning dose only on the first dose date and on Cycle 2, Day 1.

On the days PK samples are to be collected, study drug administration must occur under the supervision of the investigator (or designee) after the predose PK sample is obtained. The date and time of study drug administration on the day (ie, evening dose) prior to Cycle 2, Day 1 and on the days PK samples are collected must be recorded on the eCRF. PK samples will only be collected from sites that are able to adequately follow the sampling, handling and processing procedures outlined in the Laboratory Manual.

Blood will be collected at the timepoints specified above. The actual date and time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Blood samples (2 mL) for PK analysis will be collected into EDTA collection tubes. Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Laboratory Manual for this study.

Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma zanubrutinib concentrations using a validated method.

Pharmacokinetics for Patients Assigned to Arm D

Sparse PK samples for zanubrutinib will be collected from patients assigned to Arm D as follows:

- **Zanubrutinib monotherapy run-in (Cycle 1 and Cycle 2):** predose (≤ 30 min prior to morning dose), and 2 hours (± 30 min) postdose for the morning dose only on the first dose date and on Cycle 2, Day 1

In addition, optional samples to evaluate the potential drug-drug interactions (DDI) between venetoclax and zanubrutinib will be assessed (see Appendix 17). For these patients, samples will be collected at the following timepoints:

- **Co-administration of zanubrutinib + venetoclax (Cycle 6, Day 1):** predose (≤ 30 min prior to morning dose) and postdose (2 hours [± 30 min], 4 hours [± 30 min], and 8 hours [± 2 hours]) following the morning zanubrutinib dose only.
  NOTE: If the sample cannot be collected on Day 1 of Cycle 6, it may be collected on Day 1 of any cycle beyond Cycle 6 (eg, Cycle 7, Cycle 10, etc), as long as the patient's current study drug regimen includes zanubrutinib 160 mg twice a day for at least 5 consecutive days and venetoclax 400 mg daily for at least 1 week prior to the day of sample collection.

For more information about the PK sub-study for patients assigned to Arm D, see Appendix 17.

5.6. Safety Assessments

Echocardiogram

An echocardiogram, multigated acquisition scan (MUGA), or gated heart pool scan (GHPS) will be performed within 90 days of enrollment (ie, a standard of care procedure performed prior to consent for this study may be used if within window), and as medically necessary.

Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, heart rate, and body temperature), and weight will be performed at each study visit during study treatment. Height (cm) is determined during any pre-dose timepoint.

A complete physical examination includes an assessment of systems per standard of care at the study site and as clinically indicated by symptoms.

Assessment of vital signs and a focused physical examination on the first day of Cycle 1 may be skipped if performed within 7 prior days.

ECOG Performance Status

ECOG performance status will be assessed at the screening visit, each visit during study treatment, and at the Safety Follow-up visit. Appendix 6 will be used to assess performance status.

Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 35 days before the first visit in Cycle 1 and since the prior study visit, thereafter. Concomitant medications should be collected at Screening, Treatment phase, Post-treatment Follow-up phase until Long-term Follow-up phase. NOTE: During the Long-Term Follow-up phase, only information on new anticancer therapy will be collected.

Adverse Events Review

Record AEs that occurred during screening on the medical history case report form and in the patient's source document.

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be collected. If patients screen fail, collection of SAEs will end at the time of screen failure.

The AE reporting period is defined in Section 8.4.1.

All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 8.1. Important additional requirements for reporting SAEs are explained in Section 8.

Tumor Lysis Syndrome Evaluations (Arm D Only)

Patients will be monitored for TLS based on their risk category. Monitoring will include evaluations of serum chemistry (including uric acid), hematology, and vital signs as specified in Section 6.2.3.1, Appendix 12, Appendix 14, and Appendix 15. TLS will be graded per the Cairo-Bishop criteria (Appendix 16).

5.7. Efficacy Assessments

Response will be assessed and categorized per the iwCLL criteria (Hallek et al, 2008) with modification for treatment-related lymphocytosis (Cheson et al, 2012; Appendix 2) for patients with CLL, and per Lugano Classification for NHL (Cheson et al, 2014; Appendix 3) for patients with SLL. Response will be assessed by independent central review, except in Cohort 3 (Arm D), which may have assessment by independent central review at the sponsor's discretion. Investigators will also assess response. The primary endpoint will be PFS based on independent central review. Response parameters will include assessment of lymphadenopathy, hepatomegaly, splenomegaly, blood lymphocyte count, bone marrow aspirate/biopsy, platelet count, hemoglobin level, and neutrophil count. For efficacy assessments, physical examination findings, and laboratory results obtained pre-dose on the first dose date should be used as baseline. If the pre-dose values on the first dose date are not available, the most recent prior values (baseline) will be used. All malignant lesions found by imaging will be recorded at baseline. Up to 6 target lesions will be recorded with measurements. The remaining lesions will be recorded as non-target lesions. Target lesion measurements will be recorded in the eCRF at each imaging timepoint in 2 perpendicular dimensions: LDi and short diameter (SDi). SDi is defined as the longest diameter perpendicular to LDi.

In the event of a treatment delay, disease assessments for response evaluation are to continue per the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12). For patients receiving zanubrutinib, refer to Appendix 2 regarding the assessment of disease progression during study drug holds.

Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms based on iwCLL criteria (Hallek et al, 2008; unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of > 10% body weight within the previous 24 weeks and since last examination) will be evaluated at screening, end of Cycle 3, then every 12 weeks for 96 weeks (approximately 24 months), then every 24 weeks thereafter (through the Treatment phase and Post-treatment Follow-up phase).

Examination of Liver, Spleen and Lymph Nodes by Physical Examination

Record presence or absence of hepatomegaly, splenomegaly, and/or lymphadenopathy at Screening, end of Cycle 3, then every 12 weeks for 96 weeks (approximately 24 months), then every 24 weeks thereafter, and during Safety Follow-up.

Computed Tomography

For patients with SLL, only the CT-based response criteria (and not the PET-CT-based response criteria) of the Lugano Classification for NHL (Cheson et al, 2014; Appendix 3) will be used.

All patients (CLL/SLL) must have baseline imaging within 35 days of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and pelvis and any other disease sites should be performed. Oral contrast is recommended unless contraindicated or not available.

For patients who have a contraindication to CT scan with IV contrast at baseline, the following imaging should be performed during Screening and on study in place of CT scan with IV contrast: MRI of the neck, abdomen, and pelvis, and non-contrast CT of the chest. For patients

who develop a contraindication to CT scan with IV contrast while on study, see the Radiology Manual for additional details about imaging requirements. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation are kept constant throughout a patient's course on study; additional details can be found in the Radiology Manual.

Imaging of the neck, chest, abdomen, and pelvis is required to be performed at screening (the "baseline" scans), and approximately every 12 weeks after the first dose date for 96 weeks (approximately 24 months), then approximately every 24 weeks, thereafter until disease progression (including for patients who have discontinued or completed study treatment), withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. For patients in Arms A, B, and C, at time of suspected disease progression, imaging should be provided to the independent central review facility as soon as possible to enable prompt central assessment for disease progression.

All malignant lesions identified by imaging at baseline and meeting the following requirements will be recorded in the eCRF: lymph node > 1.5 cm in at least one dimension, or non-nodal lesion measuring at least 1 cm x 1 cm. Up to 6 of the lesions with bi-dimensional measurements will be identified as 'target' lesions. The remaining lesions, whether measurable or non-measurable, will be recorded as 'non-target' lesions. For target lesions, measurements will be recorded in the eCRF at each imaging timepoint in 2 perpendicular dimensions: LDi and SDi. LDi is the longest diameter, and SDi is the longest diameter perpendicular to LDi. Multiple non-target lesions co-located in the same anatomical region may be classified under a single non-target annotation. Examples of non-target lesions include:

- Any measurable nodal disease beyond the maximum number of six (6) target lesions
- Extranodal disease beyond the maximum number of six (6) target lesions
- Assessable disease that is non-measurable
- All bone lesions, irrespective of the modality used to assess them
- Cutaneous lesions
- Gastrointestinal disease
- Kidneys
- Irradiated lesions
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites

At each imaging timepoint, target lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded, even when very small (eg, 2 mm). However, sometimes lesions become so faint on a scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure (TSTM)." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm

should be assigned (NOTE: it is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). For lesions where the longest diameter is measurable, but the longest perpendicular measurement is not, enter the longest diameter into the EDC; the longest perpendicular measurement should be recorded as "too small to measure" with a default value of 5 mm.

At each timepoint, the presence of new lesions should be assessed as per the criteria below:

- A new lymph node > 1.50 cm in any axis
- A new extranodal site > 1.0 cm in any axis, OR if ≤ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to CLL/SLL
- Assessable disease of any size unequivocally attributable to lymphoma

Other clinical factors that could result in the temporary appearance of a new lesion (ie, infection) should be ruled out before reporting disease progression.

All CT scans, and MRIs obtained during the study will be collected and may be reviewed by an independent central review identified to this trial. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, independent central review).

In rare instances the timing of a patient's scans may fall outside the imaging procedure window specified in the protocol Schedule of Assessments – for example, due to out-of-town travel or other unforeseen circumstances. Rare occurrences of missing scans will not necessarily be considered as a protocol deviation; the Sponsor will make the final determination. 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.

Bone Marrow Examination

A bone marrow core biopsy is required within 90 days before enrollment. Confirmed availability of bone marrow biopsy slides is required at time of enrollment. In lieu of performing a bone marrow procedure, a site can submit 10 slides from a previously performed diagnostic bone marrow biopsy, if available. For patients with SLL, bone marrow aspirate may be provided for the central del17p FISH testing in addition to the peripheral blood sample:

- If both peripheral blood and bone marrow aspirate samples have a valid central lab test result for del17p and the results are discrepant, the result from the bone marrow aspirate sample will be used for study enrollment.
- If only the peripheral blood sample has a valid central lab test result for del17p, the result from the peripheral blood sample will be used for study enrollment. No additional samples will be tested in the central lab.
- If only the bone marrow aspirate sample has a valid central lab test result for del17p, the result from the bone marrow aspirate sample will be used for study enrollment. No additional samples will be tested in the central lab.

Bone marrow core biopsy and aspirate are required under the following conditions during the treatment period and Post-treatment Follow-up phase starting at Week 36:

- If clinical and laboratory results demonstrate a potential CR or CRi, to confirm a CR or CRi (minimal residual disease assessment will also be assessed in the bone marrow and/or blood at this time);

In cases of progression of cytopenias unrelated to autoimmune cytopenias or study treatment, perform a bone marrow biopsy and aspirate to confirm progressive disease. NOTE: The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia). This is documented by a decrease of hemoglobin (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 at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.

All the bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory. If a bone marrow examination was not submitted to the central pathology laboratory per protocol, was submitted centrally and was not evaluable, or a procedure was performed as part of standard of care at any time, please document the results in the eCRF if local pathology results are available.

In addition, sites have the option to submit other specimens that may provide evidence of disease progression, such as tissue biopsy or blood sample, to the central pathology lab for analysis (ie, Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).

After Week 36, for all study arms, bone marrow core biopsy and aspirate are required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed. For Arms A, B, and C, once CR or CRi in the bone marrow has been confirmed, no further bone marrow core biopsy and aspirate are required unless otherwise clinically indicated.

For Arm D only, patients with suspected CR or CRi whose bone marrow core biopsy shows morphologic evidence of disease may optionally undergo another bone marrow core biopsy and aspirate approximately 24 weeks from the most recent previous bone marrow examination. It is recommended to do this assessment if the patient has two consecutive tests showing negative peripheral blood minimal residual disease (MRD; see Section 5.10).

Patients in Arm D will have serial monitoring for undetectable MRD4 status at each scheduled response assessment (see Section 5.10).

5.8. Patient-Reported Outcomes

PROs will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients must complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12) before the first dose of study drug is administered and prior to study drug administration on subsequent PRO timepoints. If feasible, patients must complete QOL questionnaires before performing any other procedures.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The Euro Qol Group 1990; Herdman et al, 2011). Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." A sample questionnaire is provided in Appendix 7 as an example only.

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties; Fayers et al, 2001). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in non-Hodgkin lymphoma patients. It is a reliable and valid measure of PRO in cancer patients and takes about 11 minutes to administer. A sample questionnaire is provided in Appendix 8 as an example only.

5.9. Laboratory Assessments

Samples for protocol-specified chemistry and coagulation profiles will be evaluated by a central laboratory. Protocol-specified hematology testing may be performed either centrally or locally and is to remain consistent (all local, or all central) throughout a patient's course on study. All protocol-required CBCs performed locally are to be recorded in the eCRF. For all patients, regardless of whether a local or central laboratory will be used for CBC testing, the "baseline" for response assessment should be the CBC values obtained predose on the first dose date. If no values are available predose on the first dose date, then the most recent CBC values from the same selected laboratory prior to the first dose date should be assigned as baseline for response assessment calculations.

For sites choosing central hematology testing, central laboratory results are required for all evaluation timepoints. In case of missing central hematology data for one or more response evaluations, a repeat sample should be sent promptly to the central laboratory. In the event that a response-evaluation timepoint is "not evaluable" due to missing central laboratory hematology value(s):

- Local hematology data, if available at all prior response assessment timepoints, should be entered into the eCRF and used for evaluation throughout the study.

With permission from the medical monitor or designee, protocol-specified central laboratory assessments may be performed locally, excluding del17p, which must be determined centrally. Additional laboratory assessments, including laboratory values required within a short timeframe on dosing days to determine drug dosage, and unscheduled laboratory tests ordered by the investigator as necessary for patient monitoring, will be performed locally where possible and

entered into the eCRF. Samples for serum immunoglobulins, pregnancy testing, and hepatitis B and C testing will be performed locally, however, they may be performed centrally in certain countries.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the laboratory manual.

Chemistry, CBC, coagulation, serum immunoglobulin, and β2-microglobulin, will be performed at the timepoints specified in the Schedule of Assessments (Appendix 10, Appendix 11, and Appendix 12), and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first study drug administration. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1.

Hematology

For instructions regarding the use of central versus local laboratories for hematology assessments, see Section 5.9.

CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential, which includes neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

CBC with differential is required to be performed every visit during the Treatment phase, and Post-treatment Follow-up phase. 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.

Chemistry

Serum chemistry 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.

Creatinine clearance may be calculated using either a local laboratory serum creatinine value or the central laboratory value.

The following 2 chemistry tests will only be done at screening and will be performed locally: direct antiglobulin test and β-2 microglobulin. NOTE: These tests may be performed centrally in certain countries.

Serum chemistry is required to be performed every visit during the Treatment phase. Serum chemistry is not required during the Post-treatment Follow-up phase except at the Safety Follow-up visit.

For patients in Cohort 3, Arm D who have electrolyte imbalances within 24 hours after the first dose of venetoclax or a venetoclax dose increase, the procedures in Appendix 15 should be followed to reduce the risk of TLS. For patients in Cohort 3, Arm D who are treated with rasburicase (see Appendix 15), uric acid must be analyzed in plasma. Rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples, potentially resulting in

spuriously low uric acid assay readings. Refer to the Laboratory Manual for special sample handling procedures to avoid ex vivo uric acid degradation.

Serum Immunoglobulins

Quantitative serum immunoglobulins (IgG, IgM, IgA) will be measured at Screening or baseline, then at Cycles 4, 7, 10, 13, and then every 24 weeks thereafter during the Treatment phase and Post-treatment Follow-up phase.

Coagulation

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.

Hepatitis B and C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. All hepatitis B and hepatitis C testing will be performed by local laboratories unless central laboratory testing is required by the site. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status). The limit of detection for HBV DNA must have a sensitivity of less than 20 IU/mL. The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible. Patients HBsAg-negative, HBcAb-positive, and HBV DNA negative must undergo HBV DNA screening PCR every 4 weeks (± 4 days) for the entire duration of study treatment. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days. If, during monitoring (every 4 weeks) of HBV DNA by PCR, the value is between 20 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drug should be stopped and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped and antiviral therapy initiated. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, the medical monitor and physicians with expertise in managing hepatitis B.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo HCV RNA screening every 4 weeks for the entire duration of study treatment. Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, the medical monitor and physicians with expertise in managing hepatitis C.

HBV and HCV monitoring must be continued until the latest protocol-required Safety Follow-up Visit for the patient's treatment arm, including crossover. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 1 below shows how the results for HBV/HCV, and HBV/HCV testing at screening relate to the inclusion and exclusion criteria.

Table 1: Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by PCR)

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA "Not detected"* *Perform monitoring of HBV DNA every 4 weeks*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*
HCV	**Antibody (-)**	
	Antibody (+) *HCV RNA "Not detected"* *Perform monitoring of HCV RNA every 4 weeks*	**Antibody (+)** *HCV RNA Detected*

Abbreviations: HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.
Patients with known HIV are excluded from the study.

Pregnancy Test

A serum pregnancy test will be performed at screening within 7 days of randomization and end of treatment in women of childbearing potential. Any female patient who is pregnant will not be eligible for the study. Urine or serum pregnancy tests will be performed by either local or central laboratory every 4 weeks (28 days) until end of treatment. For patients on zanubrutinib (Arms A, C, D, and B after crossover), patients should be tested at the 30-day safety follow up and at 60 and 90 days after the end of treatment (see Appendix 10, Appendix 11, and Appendix 12 for collection windows). For patients on bendamustine and rituximab (Arm B before crossover), patients should be tested at the 30-day safety follow-up, at 60 days after the end of treatment, and at the 90-day safety follow up (see Appendix 10, Appendix 11, and Appendix 12 for collection windows). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from study treatment.

5.10. Biomarkers

CLL/SLL is characterized by a plethora of mutations shown to be linked to favorable prognosis (eg, del13q, hyper-mutation of IGHV) or poor prognosis (eg, del11q, del17p, unmutated IGHV, mutations in TP53, ATM and Notch 1). Prospective baseline biomarker test results for del17p and IGHV are required for enrollment. A single valid test result by central laboratory for del17p and a single valid test result by either central or local laboratory for IGHV are needed for enrollment.

Therefore, all patients will provide blood samples at the time of screening to assess chromosomal abnormalities (eg, del17p, del11q, and del13q, and to determine Trisomy 12) by FISH and the mutation status of relevant genes (including, but not limited to, IGHV and TP53), using a specialized central laboratory. IGHV mutational status will also be determined by molecular techniques using blood in a specialized central laboratory or in a local laboratory. Blood samples

will also be used for cytogenetic analysis to assess complex karyotype, as well as to establish baseline characteristics by flow cytometry.

Testing for IGHV mutational status may use either the PCR/Sanger IGHV assay, or a next generation sequencing (NGS) immunoglobulin heavy chain (IGH) assay. Local IGHV testing may be used for this study and may be performed outside of the 35-day screening window but not greater than 90 days. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor if the date of the results for either the del17p or IGHV will be ≥ 90 days before enrollment to ask whether re-testing of baseline del17p or IGHV is needed.

For Arm D only, patients must have a central laboratory FISH test for del17p performed. A patient with a result other than "with del17p" may be eligible only if the patient has a pathogenic TP53 variant previously documented per local laboratory test meeting the criteria specified in Appendix 18. Approval for enrollment by the medical monitor is required. In addition, if the local TP53 test used a sample other than peripheral blood, a specimen from that same tissue sample, if available, should be sent to the central laboratory for potential future central TP53 testing.

For Arms A, B, and C, at the time of confirmed clinical CR or CRi, minimal residual disease will be assessed using a peripheral blood sample collection and the bone marrow aspirate that was provided for clinical confirmation of CR.

For Arm D only, starting at Week 12, peripheral blood samples will be collected at every scheduled response assessment for undetectable MRD4 analysis.

- Patients with confirmed CR or CRi and 2 consecutive tests showing undetectable MRD in peripheral blood ≥ 12 weeks apart will undergo bone marrow aspiration for MRD assessment. Patients will undergo repeat bone marrow aspirate every approximately 48 weeks until 2 consecutive tests (≥ 12 weeks apart) show undetectable MRD, as long as peripheral blood MRD also remains negative.
- It is recommended, but not required, to undergo repeat bone marrow aspirate approximately every 12 weeks after the first bone marrow MRD assessment, until 2 consecutive tests (≥ 12 weeks apart) show undetectable MRD, as long as peripheral blood MRD also remains negative.
- After Week 112, if bone marrow aspirate continues to show detectable MRD, patients who remain in CR or CRi and have continued peripheral blood MRD negativity may optionally undergo bone marrow aspirates for assessment of MRD. These bone marrow aspirates may be collected every approximately 24 weeks, until 2 consecutive tests (≥ 12 weeks apart) show undetectable MRD.

- Patients requiring additional bone marrow assessments for MRD only require aspirate – no core biopsy is required except when clinically indicated (see Section 5.7).
- Once patients have 2 consecutive bone marrow aspirates (≥ 12 weeks apart) showing undetectable MRD, no additional aspirate is necessary except when clinically indicated (see Section 5.7).

Patients receiving zanubrutinib who have progressive disease will be asked to provide a blood sample for the assessment of relevant BTK pathway genes for specific mutations that have been identified as markers of resistance (such as, but not limited to, BTK and PLCγ) as well as for the assessment of markers using next-generation sequencing (NGS) methodologies. This sample is optional. Also, optional testing of other tissue samples (eg, lymph node biopsy) may be submitted at the time of disease progression for assessment of resistance mutations.

5.11. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include vital signs/focused physical examination; ECOG performance status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; hematology and chemistry laboratory assessments, and bone marrow examination. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

5.12. Treatment Phase and Post-treatment Follow-Up Phase

For all arms, the Treatment phase starts with the first day of assigned study treatment and continues until the last dose of drug has been taken/received.

Patients must discontinue study drug for any one of the following reasons:

- Disease progression confirmed by independent central review (or by investigator assessment for patients in Cohort 3 [Arm D])
  - With medical monitor approval, patients with disease progression may continue study drug treatment until the start of next-line therapy or while the patient is receiving clinical benefit
- Patient withdrew consent
- Positive pregnancy test

Additionally, patients may discontinue study drug for any one of the following reasons:

- Adverse event(s)
- Investigator decision
- Other

Patients may voluntarily withdraw consent from treatment at any time.

For all arms the Post-treatment Follow-up phase begins the day after the last dose has been taken and ends at the time of progressive disease.

The schedule of visits and procedures for Post-treatment Follow-up is the same as for the Treatment period with the exception that chemistry laboratory values will not be collected during Post-treatment Follow-up. All other safety and efficacy assessments will be performed during Post-treatment Follow-up (see Schedules of Assessments, Appendix 10, Appendix 11, and Appendix 12).

5.13. Arm B "Crossover" Treatment with Zanubrutinib

At investigator discretion, and with BeiGene medical monitor approval, patients in Arm B of Cohort 1/1a may "crossover" to receive next line treatment with single agent zanubrutinib following disease progression confirmed by independent central review. Initiation of crossover therapy must occur after central confirmation of progression and prior to the start of any other CLL/SLL therapy. To initiate crossover therapy with zanubrutinib, a patient must meet the safety and laboratory test requirements documented below and then return to the Treatment Phase of the study. These patients will follow the required safety and laboratory procedures for the zanubrutinib Schedule of Assessments (Appendix 10) while receiving zanubrutinib. After crossover, tumor response will only be evaluated by the investigator. Patients who crossover from Arm B do not need to have PK samples or PROs collected.

To request crossover treatment with zanubrutinib, site staff will complete the Request for Crossover Treatment form and submit to the medical monitor for approval following independent central review confirmation of disease progression. Documentation must be provided showing that the patient meets the following requirements within 15 days before date of submission of the form:

- Platelets $\geq 50{,}000/mm^3$; (NOTE: the screening platelet count may be obtained post-transfusion)
- ANC $\geq 750/mm^3$; (NOTE: growth factor use is allowed to meet ANC requirement)
- AST and ALT ≤ 2 x ULN
- Serum total Bilirubin < 2.5 x ULN (not required for cases with documented Gilberts Syndrome)
- QTcF ≤ 480 msec, site to provide copy of ECG tracing and rhythm
- No known New York Heart Association Class III or IV congestive heart failure
- Creatinine clearance ≥ 30 mL/min
- HBV and HCV serology confirming absence of infection. Patients with evidence of potential infection (eg, HBcAb positive or HCV antibody positive) are required to complete viral load testing to confirm eligibility (refer to "Hepatitis B and C Testing" in Section 5.9)

The investigator will confirm that the above crossover requirements are met and that the patient qualifies to initiate full dose zanubrutinib at 160 mg twice daily. The investigator must also ensure that the laboratory and safety tests required above for crossover and imaging of the neck, chest, abdomen, and pelvis, as indicated in Section 3.1, are completed within 90 days of initiating crossover study drug treatment. Any patient being considered for crossover who does not initiate crossover treatment within approximately 3 months after independent central review-confirmed disease progression should be contacted either by clinic visit or by phone approximately every 12 weeks to check the survival status and for any new second primary malignancy, to confirm if the patient is still interested in the crossover treatment, and to confirm whether the patient has started any non-protocol CLL/SLL anticancer therapy. Contact the medical monitor for any patient being considered for crossover who, based on the protocol dose

modification section, would be required to implement a dose modification or a delay in the initial dosing of zanubrutinib.

5.14. Safety Follow-Up Visit

All patients who permanently discontinue study drug will have a Safety Follow-up visit approximately 30 days after the last dose of study drug to collect AEs, including AEs that may have occurred or been ongoing after the patient discontinued study treatment. The Safety Follow-up visit may be combined with a required Post-treatment Follow-up clinic visit so long as both visits adhere to the specified visit windows in the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12). Patients who received bendamustine will have a second safety follow-up visit approximately 90 days after the last dose of bendamustine. The investigator or his/her designee will continue to collect all AEs and SAEs in the post-treatment phase and continue to collect information on new anticancer therapy given after the last dose of study drug. The Safety Follow-up visit is required even if patient is still in the Cycle 1 - 7 period. Refer to the Schedules of Assessments (Appendix 10, Appendix 11, and Appendix 12) for the assessments to be performed at the Safety Follow-up visit.

5.15. Long-Term Follow-Up

Patients will enter Long-term Follow-up the day after documented disease progression confirmed by independent central review (or by investigator assessment for patients in Cohort 3 [Arm D]). NOTE: Patients in Arm B who receive approval for and initiate next-line "crossover" therapy with zanubrutinib will follow the Schedule of Assessments for Arms A and C (Appendix 10) instead of entering Long-term Follow-up after disease progression (see Section 5.13). Patients who initiate next-line ("crossover") treatment with zanubrutinib will enter Long-term Follow-up at the time of subsequent disease progression after starting zanubrutinib per investigator assessment. Response assessments after crossover will occur per investigator assessment and will not be performed by independent central review.

Patients in Long-term Follow-up will be followed for their next CLL/SLL anticancer therapy including date of progression following next line therapy, and for survival. Contact will be in person or via phone (with the patient's guardian, if applicable) every 12 weeks until study end.

5.16. End of Study

Reasons for complete withdrawal from the study (including treatment and all follow-up visits) will occur under the following circumstances:

- Patient withdrew consent
- Death
- Study termination by sponsor
- Other

Patients may voluntarily withdraw consent from the study at any time.

5.17. Lost to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow-up during the study to complete study-related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up.

6. STUDY TREATMENT

6.1. Study Treatment Preparation and Dispensation

6.1.1. Packaging and Labeling

Zanubrutinib capsules will be provided in a child-resistant high-density polyethylene (HDPE) bottle with induction seal and bottle label. Rituximab and bendamustine will be provided by the sponsor or via local procurement by the site, in vials containing solution and vials containing powder for concentrate for solution for infusion, respectively. Venetoclax tablets will be provided by the sponsor or via local procurement by the site.

The contents of the study treatment labels will be in accordance with all applicable local regulatory requirements.

All study treatments will be consistent with those described in the Pharmacy Manual for this study.

6.1.2. Handling and Storage

The IRT system will be used for drug supply management. The study drugs will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel, and kept under physical conditions that are consistent with study drug-specific requirements. The study drugs must be kept at the temperature condition as specified on the labels.

Zanubrutinib bottles must be stored at room temperature 15ºC to 30ºC (59°F to 86°F).

Bendamustine may be stored up to 25°C (77°F), with excursions permitted up to 30°C (86°F; see USP Controlled Room Temperature). Please refer to the drug label for any additional local storage requirements. Retain bendamustine in its original packaging until time of use, to protect it from light.

Rituximab vials (100 mg and 500 mg) are stable at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date stamped on the carton. Rituximab vials should be protected from direct sunlight. Do not freeze or shake. Rituximab solutions for infusion may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature; however, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C to 8°C).

Venetoclax should be stored at or below 30°C (86°F).

Study drugs must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive study drug(s), in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug(s).

For situations where sites are locally sourcing the comparators, patient visit information may still be collected to IRT.

6.1.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian. For the purposes of the interim and final analyses, patients may be contacted in between visits to collect drug accountability data, which will be included in the EDC system. Compliance for Arm D should be performed at the start of each new cycle of zanubrutinib or combination zanubrutinib plus venetoclax until the completion of venetoclax dosing. Following completion of venetoclax, compliance for zanubrutinib will be assessed at each patient visit per the schedule of assessments.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. All patients enrolled in the study will be provided with patient diaries. The patient is responsible for maintaining the patient diary. The patient will record the date, time, and number of capsules ingested. If capsules are missed at any timepoint, patient will record number of capsules missed and reason. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor (or locally sourced), the amount supplied, and/or administered to and returned by patients, if applicable.

6.1.4. Disposal and Destruction

After completion of the study, and following final drug inventory reconciliation by the monitor, the study site will destroy or return all unused study drug supplies. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.2. Dosage and Administration

6.2.1. Zanubrutinib

For patients in Arms A and C, zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the Treatment phase as detailed in the Pharmacy Manual. For Arm D patients, dispensation and accountability for zanubrutinib will occur every cycle and may require patients to return to the site/pharmacy each cycle while venetoclax is being administered. The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Patients will be requested to bring their unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and administered to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Patients in Arms A and C (zanubrutinib) and D (venetoclax + zanubrutinib) should be instructed that if a dose of the study drug is not taken at the scheduled time, they should skip the study drug if the time to next dose is 8 hours or less, and return to normal dosing with next dose. If a patient vomits after taking the zanubrutinib capsules, that dose should not be repeated.

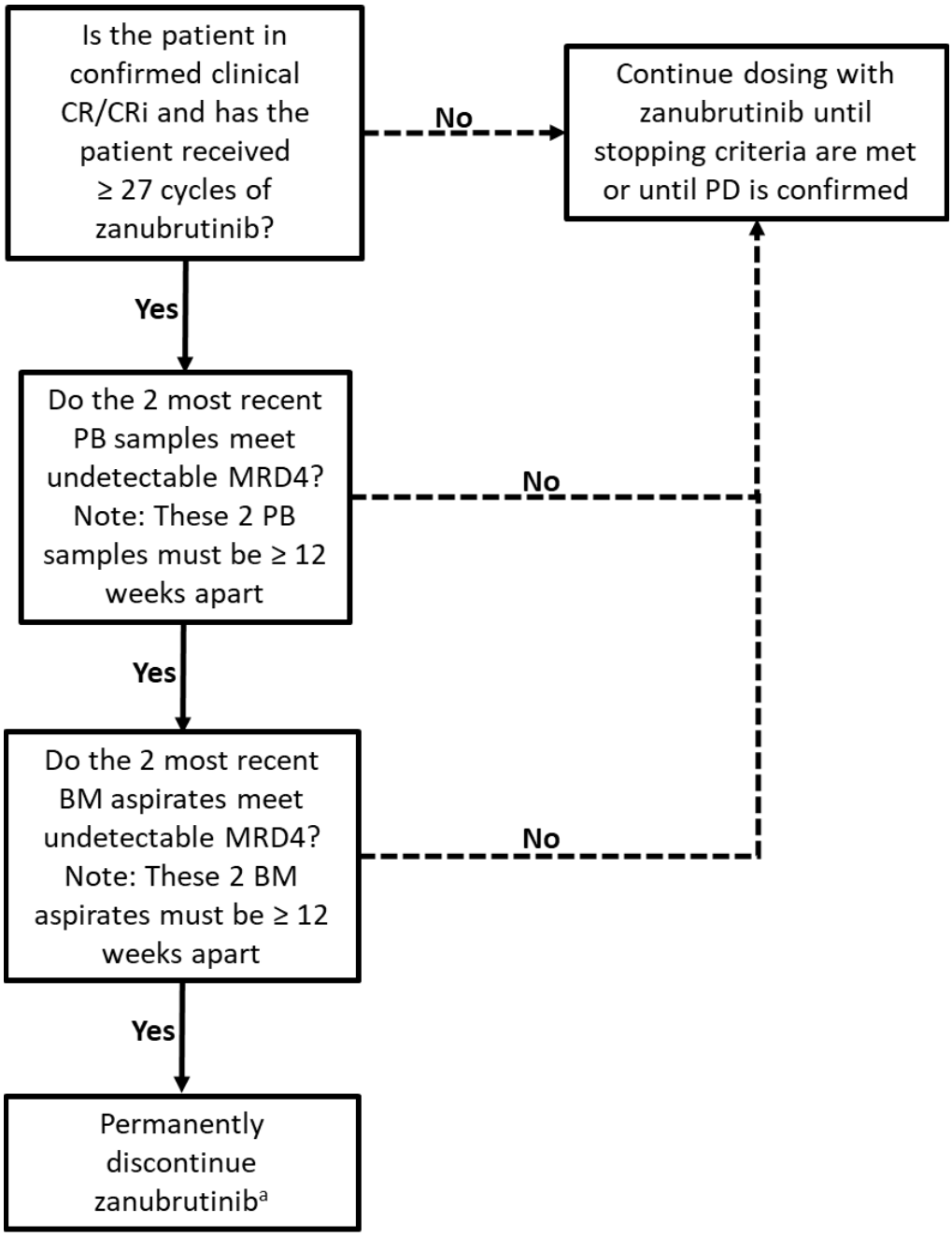
On the days of zanubrutinib PK blood sampling, study drug administration for patients assigned to Arm A (Cohort 1/1a), Arm C (zanubrutinib), and Arm D (zanubrutinib monotherapy run-in) will occur at the center after the predose blood sampling has occurred under the supervision of the investigator or his/her designee. The investigator or his/her designee must instruct the patient not to self-administer the study drug prior to the office visit on those days.

Unless otherwise agreed with the medical monitor, patients in Arm D will stop zanubrutinib at any time on or after Week 112, Day 1 if all of the following conditions are met simultaneously:

- Patient is in confirmed CR or CRi
- Patient has undetectable minimal residual disease by undetectable MRD4 in peripheral blood on the 2 most recent consecutive tests, performed ≥ 12 weeks apart.
- Patient has undetectable minimal residual disease by undetectable MRD4 in bone marrow aspirate on the 2 most recent consecutive tests, performed ≥ 12 weeks apart.

Patients not meeting the above criteria will continue zanubrutinib until progression of disease, unacceptable toxicity, or end of study. See Figure 2 for a zanubrutinib dose-decision flow chart.

Figure 2: Zanubrutinib Dose Decision Matrix (Arm D only)



CR, complete response; CRi, complete response with incomplete hematopoietic recovery; BM, bone marrow; PB, peripheral blood; undetectable MRD4, undetectable minimal residual disease at $< 10^{-4}$ sensitivity

[a] If any unscheduled PB or BM aspirates are collected during the gap between the BM aspirates, the patient must not have any PB or BM samples that are positive for minimal residual disease in order to discontinue zanubrutinib.

6.2.2. Bendamustine and Rituximab

Patients in Arm B will receive B+R. Bendamustine will be administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles. The final prepared bendamustine dose may be rounded (must be within 94% to 106% of the precise calculated dose).

Rituximab will be administered intravenously at a dose of 375 mg/m^2 on Day 0 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2 to 6. For patients at risk for infusion-related reaction, dose may be administered as follows: For Cycle 1, rituximab may be administered on Day 0, or the total rituximab dose may be delivered over 2 consecutive days on Days 0 and 1, or on Days 1 and 2. For Cycles 2 to 6, rituximab may be administered on Day 1, or the total rituximab dose may be delivered over 2 consecutive days on Days 1 and 2. The final prepared rituximab dose may be rounded (must be within 100% to 110% of the precise calculated dose). For the first infusion, rituximab should be initiated at a rate of 50 mg/hour. In the absence of infusion toxicity, the infusion rate should be increased in 50 mg/hour increments at 30-minute intervals to a maximum of 400 mg/hour. For subsequent infusions, rituximab can be initiated at a rate of 100 mg/hour, and in the absence of infusion toxicity, the infusion rate can be increased in 100 mg/hour increments at 30-minute intervals to a maximum of 400 mg/hour. Patients should be premedicated prior to each rituximab infusion with acetaminophen, antihistamine, with or without a glucocorticoid as per institutional standards.

6.2.3. Venetoclax

Venetoclax will be dispensed by the study center personnel to patients every cycle to ensure adequate drug supply for administration at home throughout the Treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Venetoclax should be taken with food. Patients will complete a pill diary daily for as long as they are on the study. Patients must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance. Patients will be requested to bring their unused medication, and all containers/packaging, to the center at each visit. All dosages prescribed and administered to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

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 4, Days 1 through 7, 50 mg on Cycle 4, Days 8 through 14, 100 mg on Cycle 4, Days 15 through 21, 200 mg on Cycle 4, Days 22 through 28, and 400 mg from Cycle 5, Day 1 onward. Venetoclax should be administered at approximately the same time as zanubrutinib.

Patients will stop venetoclax at any time after Week 64, Day 1 if all of following conditions are met simultaneously:

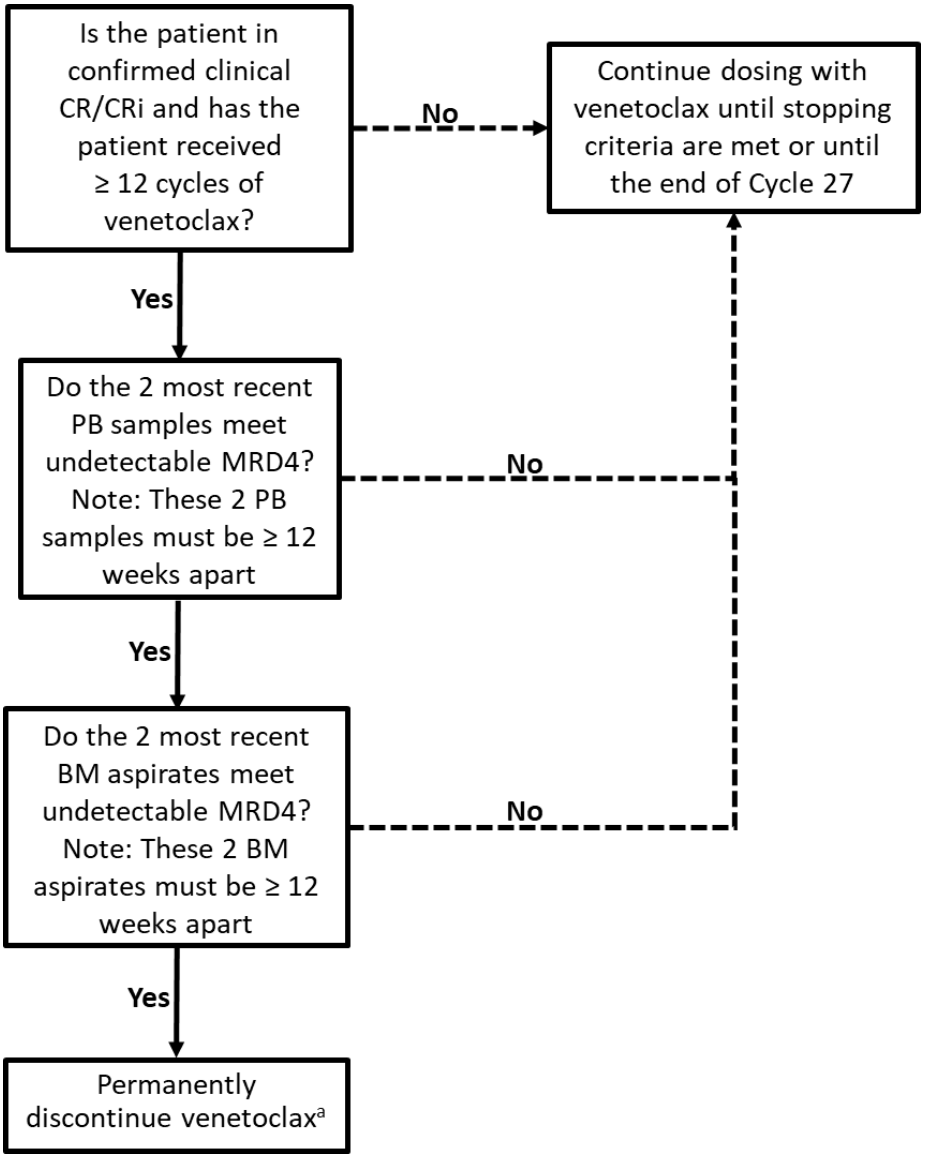
- Patient is in confirmed CR or CRi
- Patient has undetectable minimal residual disease by undetectable MRD4 in peripheral blood on the 2 most recent consecutive tests, performed ≥ 12 weeks from each other.
- Patient has undetectable minimal residual disease by undetectable MRD4 in bone marrow aspirate on the 2 most recent consecutive tests, performed ≥ 12 weeks from each other.

Patients on venetoclax who stop due to confirmed MRD negativity will remain on zanubrutinib until at least Week 112, Day 1, unless the patient has progression of disease or unacceptable toxicity.

All other patients that remain on venetoclax will stop venetoclax prior to Week 112, Day 1 (total of 96 weeks [approximately 24 months] of venetoclax), unless the patient has progression of disease, unacceptable toxicity, or the study ends. See Figure 3 for a venetoclax dose-decision flow chart. These patients will also continue on zanubrutinib until achievement of confirmed MRD negativity, progression of disease, unacceptable toxicity, or end of study.

Patients with previously confirmed MRD negativity who met the dose stopping criteria and are no longer receiving venetoclax and zanubrutinib will not be permitted to restart either venetoclax or zanubrutinib if they are shown to have detectable MRD in a subsequent peripheral blood or bone marrow aspirate sample. Patients with previously confirmed MRD negativity who met the dose stopping criteria for venetoclax but are still receiving zanubrutinib should continue to receive zanubrutinib if they are shown to have detectable MRD in a subsequent peripheral blood or bone marrow aspirate sample.

Figure 3: Venetoclax Dose Decision Matrix (Arm D only)



CR, complete response; CRi, complete response with incomplete hematopoietic recovery; BM, bone marrow; PB, peripheral blood; undetectable MRD4, undetectable minimal residual disease at $< 10^{-4}$ sensitivity
[a] If any unscheduled PB or BM aspirates are collected during the gap between the BM aspirates, the patient must not have any PB or BM samples that are positive for minimal residual disease in order to discontinue venetoclax.

6.2.3.1. Initiation of Venetoclax and Prophylaxis/Management of Tumor Lysis Syndrome

To mitigate potential serious complications of TLS, patients will require close clinical and laboratory monitoring. See sections below for details of the TLS prophylaxis and monitoring guidelines.

TLS is a risk for patients with lymphoma who are treated with high-cell-killing agents. Clinical data from CLL patients treated to date with venetoclax suggest that patients with baseline lymph nodes ≥ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes < 5 cm. In addition, the data showed that creatinine clearance of < 80 mL/min at screening was a secondary risk factor for TLS. A detailed description of risk factors for developing TLS following treatment with venetoclax is available in the venetoclax label.

The section below describes the management of patients during venetoclax 5-week dose ramp-up based on their risk factors for developing TLS identified upon study entry.

On the basis of the data review performed by the sponsor, the following are three identified TLS risk categories:

1. **TLS low risk**: The presence of all measurable lymph nodes with the largest diameter < 5 cm by radiographic assessment and absolute lymphocyte counts < 25 x 10^9/L
2. **TLS medium risk**: The presence of all measurable lymph nodes with the largest diameter ≥ 5 cm and < 10 cm by radiologic assessment or absolute lymphocyte count ≥ 25 x 10^9/L
3. **TLS high risk**: The presence of any lymph node with the largest diameter ≥ 10 cm by radiologic assessment or the presence of both an absolute lymphocyte count ≥ 25 x 10^9/L and a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment (NOTE: Non-splenic extranodal lesions may be utilized to assess TLS risk at the discretion of the investigator.)

All patients assigned to Arm D of the study will be assessed both at screening and at the end of Cycle 3 and categorized in a TLS risk category as described above. The assessment of TLS risk categories at the end of Cycle 3 must be completed before dosing with venetoclax is initiated, therefore, Cycle 3 may be longer than 28 days.

The end of Cycle 3 TLS risk assignment will be used to guide TLS prophylaxis and monitoring. There is a possibility that patients may downgrade their TLS risk category with reduction in disease burden after 3 cycles of zanubrutinib. Therefore, the screening TLS risk assignment will be documented to determine whether induction therapy reduces TLS risk assignment, but will not be used to determine TLS prophylaxis and monitoring with addition of venetoclax. Further details of TLS prophylaxis and monitoring are presented in the summary in Appendix 14 and Appendix 15. Criteria for the diagnosis and grading of TLS are provided in Appendix 16.
NOTE: Patients should initiate venetoclax only after completing the end of Cycle 3 imaging

studies and hematology performed prior to the ramp-up period to determine TLS risk. Any exceptions should be approved in advance by the medical monitor.

NOTE: For patients who are assigned to the high TLS risk category because they present with a measurable lymph node with the largest diameter ≥ 5 cm and < 10 cm and an absolute lymphocyte count ≥ 25 x 10^9/L: investigators may reassess TLS risk and downgrade patients to TLS medium risk if the absolute lymphocyte count decreases to < 25 x 10^9/L during the ramp-up period.

6.2.3.1.1. Initial Doses: 20 mg and 50 mg

All patients, irrespective of their TLS risk category, must return to the clinic at the start of each week during the ramp-up period to receive the following TLS prophylaxis measures prior to the initiation of the first doses of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued for the duration of the ramp-up period. NOTE: Oral uric acid reducer can be continued beyond the ramp-up period as clinically indicated.
- Oral hydration consisting of fluid intake of approximately 1.5-2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose.
- Serum chemistry (NOTE: for TLS monitoring, uric acid is required but liver function panels are not required) and hematology laboratory samples (performed locally) must be drawn any time within 4 hours prior to the first dose at each dose increase and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, the first dose of venetoclax must be delayed until resolution and management. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing. 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 initiated.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows:

TLS Low Risk

Low-risk patients will receive their initial doses of 20 mg and 50 mg as outpatients.

For patients unable to maintain oral hydration at 1.5 to 2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure that this full amount of hydration is achieved. In patients for whom volume overload is considered a significant risk, hospitalization should be considered.

Serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), and after dosing (between 6-8 hours and at 24 hours [± 2 hours]). Laboratory samples should be sent for immediate analysis. 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 initiated.

The chemistry results taken between 6-8 hours after dosing must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have creatinine clearance ≥ 80 mL/min will receive their initial doses of 20 mg and 50 mg as outpatients. For patients with creatinine clearance < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator), it is recommended that they be handled as high-risk patients (see the TLS High Risk section for details of hydration, laboratory values, etc).

In addition to oral hydration stated above, IV hydration (1.5 L to 2 L) may be considered in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

Serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), and after dosing (between 6-8 hours and at 24 hours [± 2 hours]). Laboratory samples should be sent for immediate analysis. 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 initiated.

The chemistry results taken between 6-8 hours after dosing must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS High Risk

High-risk patients will be hospitalized to receive their initial doses of 20 mg and 50 mg. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after.

Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of approximately 2 L to 3 L per day or as clinically appropriate.

In addition to receiving an oral uric acid reducer, rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (ie, glucose 6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the investigator. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Appendix 15.

Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (at 4 and 8 hours [± 30 min], and at 12 and 24 hours [± 2 hours]). These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. 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 initiated. The 24-hour postdose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug. Additional laboratory assessments may be performed per investigator discretion.

6.2.3.1.2. Subsequent Dose Increases During the Venetoclax Ramp-Up Period: 100 mg and 200 mg

All patients, irrespective of their risk category, must return to the clinic at the start of each week during the ramp-up period to receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continued administration of an oral uric acid reducer for the duration of the ramp-up period as indicated above. NOTE: Oral uric acid reducer can be continued beyond the ramp-up period as clinically indicated.
- Oral hydration consisting of fluid intake of approximately 1.5 L to 2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry (NOTE: for TLS monitoring, uric acid is required but liver function panels are not required) and hematology laboratory samples (performed locally) must be drawn within 4 hours prior to the first dose at each dose increase and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to each dose increase of venetoclax or the patient should receive additional prophylactic treatment prior to dosing. If clinically significant laboratory

abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution and management. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing. 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 initiated.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows:

TLS Low Risk

Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg) as outpatients.

Serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (between 6-8 hours). Laboratory samples should be sent for immediate analysis. 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 initiated.

The chemistry results taken between 6-8 hours after dosing must be reviewed before the patient leaves the outpatient clinic that day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have creatinine clearance < 80 mL/min will receive their subsequent dose increases as outpatients. Patients with creatinine clearance < 80 mL/min and/or who have high tumor burden (defined per the discretion of the investigator) may be hospitalized.

For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (between 6-8 hours). Laboratory samples should be sent for immediate analysis. 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 initiated.

The chemistry results taken between 6-8 hours after dosing must be reviewed before the patient leaves the outpatient clinic that day.

Additional laboratory assessments may be performed per investigator discretion.

For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (at 4 and 8 hours [± 30 min] and at 12 and 24 hours [± 2 hours]). These samples are to be sent immediately to the

laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

IV hydration may be considered with a target of approximately 2 to 3 L per day or as clinically appropriate for patients who are hospitalized.

TLS High Risk

High-risk patients with creatinine clearance of ≥ 80 mL/min will receive the subsequent dose increases as outpatients. Patients with creatinine clearance < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continuing for 24 hours after.

IV hydration (1.5 L to 2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2 L to 3 L per day or as clinically appropriate.

For patients not hospitalized, serum chemistry, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (between 6-8 hours and at 24 hours [± 2 hours]). Laboratory samples should be sent for immediate analysis.

The chemistry results taken between 6-8 hours after dosing must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and, as clinically indicated (eg, if the patient is hospitalized), vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and after dosing (at 4 and 8 hours [± 30 min] and at 12 and 24 hours [± 2 hours]). These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. 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 initiated. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Additional laboratory assessments may be performed per investigator discretion.

6.2.3.2. Management of Tumor Lysis Syndrome

Criteria and grading for diagnosis of laboratory and clinical TLS are given in Appendix 16. Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix 15.

Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level after discussion with the study medical monitor based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if the dose is held more than 7 days, with the exception of initial dose level of 20 mg (for example, 200 mg will be reduced to 100 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

6.2.3.3. Tumor Lysis Syndrome Prophylaxis and Monitoring Measures

TLS prophylaxis and monitoring measures are summarized in Appendix 14 and Appendix 15.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol, whether accidental or intentional, is considered to be an overdose. Any overdose of study drug should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. **Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.5.1.** There is no specific antidote for zanubrutinib. In an event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

6.4. Precautions

For information on warnings and precautions for bendamustine, rituximab, and venetoclax refer to the prescribing information for these agents.

Male patients should be advised about sperm conservation before treatment with bendamustine or venetoclax due to possible irreversible infertility.

6.4.1. Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment with zanubrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding. Bendamustine and rituximab should also be interrupted, if applicable.

6.5. Dose Interruption and Modification

The guidelines set forth in Table 2 should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.5.1) or nonhematologic (Section 6.5.2) toxicities.

Table 2: Zanubrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Zanubrutinib dose[a] (Arms A, C, and D [zanubrutinib monotherapy run-in])
First	0 = starting dose	Restart at 160 mg twice daily
Second	-1 dose level	Restart at 80 mg twice daily
Third	-2 dose level	Restart at 80 mg once daily

Toxicity occurrence	Dose level	Zanubrutinib dose[a] (Arms A, C, and D [zanubrutinib monotherapy run-in])
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

[a.] These zanubrutinib dose modifications apply to Arms A and C and also to Arm D during the zanubrutinib monotherapy run-in

Zanubrutinib may be restarted upon resolution of toxicity and per investigator discretion if held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the sponsor's medical monitor. If, in the investigator's opinion, it is in the patient's best interest to re-escalate the zanubrutinib dose after dose reduction, then written approval must be obtained from the medical monitor.

Temporary drug holds may cause short term worsening of disease. Please review note at the end of Appendix 2 when assessing disease after a drug hold.

6.5.1. Zanubrutinib Dose Reductions for Hematologic Toxicity

Hematologic toxicity will be based on the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 9).

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness:

- Grade 4 neutropenia that is persistent for at least 10 consecutive days
- Grade 4 thrombocytopenia that is persistent for at least 10 consecutive days
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

The dose hold should start on the day that one of the above conditions is met. For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

If the same event reoccurs, patients will restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions will be allowed. Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention should be discussed with medical monitor.

Asymptomatic treatment-related lymphocytosis should not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

6.5.2. Zanubrutinib Dose Reductions for Nonhematologic Toxicity

Table 3: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Re-start Dose[a]
≥ Grade 3 bleeding not considered related to study drug	Hold until recovery to less than or equal to Grade 1	Re-start at either the original dose or dose level (-1), at the discretion of the treating investigator
≥ Grade 3 bleeding considered related to study drug	Hold until underlying condition has fully resolved. If underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib. The drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition or reason for the bleeding can be fully treated (eg, gastric ulcer resulting in GI bleed, use of anti-coagulation) and the risk of a re-bleed is deemed acceptable by the medical monitor and investigator.	Re-start at dose level (-1)
Any grade intracranial hemorrhage	Hold and assess the risk of rebleeding; if the risk of rebleeding is deemed unacceptable, permanently discontinue.	May be re-started only with medical monitor approval. See below.
Atrial fibrillation (AF) that is symptomatic and/or incompletely controlled	Hold until AF is controlled	Re-start at either the original dose or dose level (-1), at the discretion of the treating investigator
Other ≥ Grade 3 toxicity considered related to study drug, including inadequately controlled hypertension (HTN) and/or liver or renal laboratory value abnormalities	Hold until recovery to less than or equal to baseline (BL) if BL is greater than Grade 1; hold until less than or equal to Grade 1 if BL is less than or equal to Grade 1.	Re-start at the original dose level
TLS	Hold until resolution or TLS resolves to at least Grade 0.	In the event of clinical TLS, contact the medical monitor.

Abbreviations: BL, baseline; HTN, hypertension; TLS, tumor lysis syndrome
[a] These zanubrutinib dose modifications apply to Arms A and C and also to Arm D during the zanubrutinib monotherapy run-in

Zanubrutinib should be held for any ≥ Grade 3 bleeding. The drug should be permanently discontinued for any related ≥ 3 Grade hemorrhage with the exception of those where the underlying condition or reason for the bleeding can be fully treated (eg, gastric ulcer resulting in

GI bleed, use of anti-coagulation) and the risk of a re-bleed is deemed acceptable by the medical monitor and investigator. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should **not be** resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anticoagulation or antiplatelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor.

For nonhematological toxicities ≥ Grade 3 (other than hypertension adequately controlled with oral medication) or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events), suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1 or baseline, and then restarted at original dose level. If the event recurs at ≥ Grade 3, study drug will be held until recovery to ≤ Grade 1 or baseline and restarted at dose level -1. If the event recurs at ≥ Grade 3 at dose level -1, study drug will be held until recovery to ≤ Grade 1 or baseline and restarted at dose level -2. If the event recurs at ≥ Grade 3 at dose level -2, the patient will be discontinued from study treatment. For patients experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.9.

6.5.3. Dose Interruptions and Modifications for Bendamustine/Rituximab

Bendamustine

Table 4: Bendamustine Dose Reduction Table

Toxicity	Action for Bendamustine*	Re-start Dose
≥ Grade 3 neutropenia, thrombocytopenia, or anemia on planned Day 1 of a cycle (first occurrence)	Postpone next cycle until neutropenia, thrombocytopenia, and anemia are less than Grade 3	Re-start at reduced dose of 70 mg/m^2
Signs of active infection on planned Day 1 of a cycle (first occurrence)	Postpone next cycle until all signs of active infection are resolved	Re-start at reduced dose of 70 mg/m^2
Second occurrence of ≥ Grade 3 cytopenia and/or active infection on planned Day 1 of a cycle	Postpone next cycle until neutropenia, thrombocytopenia, and anemia are less than Grade 3, and all signs of active infection are resolved.	Re-start at reduced dose of 50 mg/m^2
Third occurrence of ≥ Grade 3 cytopenia	Permanently discontinue bendamustine	Not applicable

Toxicity	Action for Bendamustine*	Re-start Dose
and/or active infection on planned Day 1 of a cycle		
Other toxicities	Contact the medical monitor and refer to the bendamustine product label	-

* When bendamustine is delayed, rituximab will be delayed for same duration

In patients whose blood counts do not recover adequately within 28 days (defined as ≥ Grade 3 neutropenia, thrombocytopenia, or anemia on Day 1 of the next cycle) or still show signs of an active infection, the next treatment will be postponed, and further cycles of therapy continued (after resolution of neutropenia, thrombocytopenia or anemia to < Grade 3, or resolution of signs of an active infection) with a reduced dose of 70 mg/m^2. If the toxicity recurs, the subsequent reduced dose is 50 mg/m^2. After a maximum of 2 such dose reductions (down to 50 mg/m^2) treatment with bendamustine will be stopped (Eichhorst et al, 2016a). For other toxicities, the bendamustine prescribing information will be referenced after discussion with the medical monitor. If bendamustine is delayed, then rituximab should be delayed as well.

Rituximab

No dose reductions for rituximab are allowed. A 28-day cycle length should be maintained, if possible. If rituximab is delayed, then bendamustine should be delayed as well.

Severe, including fatal, infusion reactions can occur with rituximab. Discontinue rituximab infusion and provide medical treatment for Grade 3 or 4 infusion reactions. For less severe infusion reactions, interrupt the infusion or slow the infusion rate. Refer to the rituximab prescribing information for dose withholding or discontinuation in response to specific toxicities associated with rituximab.

6.5.4. Dose Interruptions and Modifications for Venetoclax/Zanubrutinib (Cohort 3 [Arm D] Only)

During any period of zanubrutinib monotherapy (including the run-in but not including periods of temporary venetoclax withholding), use the dose interruption and modification rules specified in Table 2 and Table 3.

The guidelines set forth below should be followed for dose interruption or modification of venetoclax and zanubrutinib for hematologic (Table 5) or nonhematologic (Table 6) toxicities and refer to dose levels of venetoclax (Table 7) and zanubrutinib (Table 8).

Table 5: Guidelines for Management of Hematologic Toxicities

Event	Action to be taken
Grade 4 neutropenia in the absence of fever or evidence of infection	**For patients who have had no prior dose reductions:** • Patients may continue on zanubrutinib and venetoclax and receive growth factor support per institutional guidelines • Prophylactic growth factor may be used in subsequent cycles. **For patients in whom neutropenia does not resolve to Grade 3 or less within 7 days despite adequate supportive care:** • Venetoclax should be withheld and CBC should be repeated every 2 to 4 days. • If neutropenia does not resolve to Grade 3 or less within 7 days after venetoclax was held then zanubrutinib should be withheld and CBC should be repeated every 2 to 4 days. • **Prophylactic growth factor** should be considered in subsequent cycles. • **For patients who have had no prior dose reductions:** For the first occurrence of hematologic toxicity, study drugs may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. • **For patients who have had one or more prior dose reductions:** Study drugs may restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. • **For patients who are at lowest available dose of zanubrutinib and/or venetoclax:** Following discussion with the study medical monitor, the patient may permanently discontinue the study drug for which no lower dose levels are available. • Following discussion with the study medical monitor, study drugs may be started sequentially with a gap of up to 7 days following dose delay for toxicity. NOTE: If cytopenia is thought to be caused mainly by CLL infiltration of the bone marrow, discuss with study medical monitor whether dose reductions are required. Study drug may be held for toxicity for up to ≤ 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the study medical monitor.

Table 5: Guidelines for Management of Hematologic Toxicities (Continued)

Event	Action to be taken
Grade 3 or 4 neutropenia with fever or evidence of infection	**For any patient with Grade 3 or 4 neutropenia with fever or evidence of infection:** • Withhold all study treatment. • Evaluate and treat febrile neutropenia per institutional guidelines. • If patient has not already initiated G-CSF, initiate G-CSF per institutional guidelines. • Prophylactic growth factor should be used in subsequent cycles. • For patients who have had no prior dose reductions: For the first occurrence of hematologic toxicity, study drugs may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. • For patients who have had one or more prior dose reductions: Study drugs may restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. • For patients who are at lowest available dose of zanubrutinib and/or venetoclax: Following discussion with the study medical monitor, the patient may permanently discontinue the study drug for which no lower dose levels are available. • Following discussion with the study medical monitor, study drugs may be started sequentially with a gap of up to 7 days following dose delay for toxicity. NOTE: If cytopenia is thought to be caused mainly by CLL infiltration of the bone marrow, discuss with study medical monitor whether dose reductions are required. Study drug may be held for toxicity for up to ≤ 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the study medical monitor.

Table 5: Guidelines for Management of Hematologic Toxicities (Continued)

Event	Action to be taken
Grade 3 or 4 hematologic toxicities (excluding neutropenia)	**For any patient with Grade 3 or 4 hematologic toxicities (excluding neutropenia):** • If Grade 3 or 4 thrombocytopenia, consider dose reduction and/or temporarily withholding anticoagulants and/or antiplatelet agents as appropriate. – If associated with bleeding, withhold all study treatment and administer RBCs or platelets as required • Venetoclax should be withheld and CBC should be repeated every 2 to 4 days. • If toxicity does not resolve to Grade 2 or less within 7 days after venetoclax was held OR if the patient is not receiving venetoclax, then zanubrutinib should be withheld and CBC should be repeated every 2 to 4 days. • **For patients who have had no prior dose reductions:** For the first occurrence of hematologic toxicity, study drugs may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. • **For patients who have had one or more prior dose reductions:** Study drugs may restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. • **For patients who are at lowest available dose of zanubrutinib and/or venetoclax:** Following discussion with the study medical monitor, the patient may permanently discontinue the study drug for which no lower dose levels are available. • Following discussion with the study medical monitor, study drugs may be started sequentially with a gap of up to 7 days following dose delay for toxicity. Asymptomatic treatment-related lymphocytosis should not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures. NOTE: If cytopenia is thought to be caused mainly by CLL infiltration of the bone marrow, discuss with study medical monitor whether dose reductions are required. Study drug may be held for toxicity for up to ≤ 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the study medical monitor.

Table 6: Guidelines for Management of Nonhematologic Toxicities

Event	Action to be taken
General guidance for treatment delays and discontinuation	• Following discussion with the study medical monitor, if the toxicity is highly likely to be attributed to a particular study drug based on the established toxicity profile of the study drug/class, the investigator may continue other study drugs as deemed clinically appropriate. • Study drug may be held for toxicity for up to ≤ 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the study medical monitor. • Following discussion with the study medical monitor, study drugs may be started sequentially with a gap of up to 7 days following dose delay for toxicity (sequenced in order of increasing likelihood of association with toxicity).
Grade ≥ 3 nonhematological toxicities (other than atrial fibrillation or hypertension)	• For other nonhematological toxicities ≥ Grade 3 suspected to be related to study drug, study drug will be held until recovery to ≤ Grade 1, and then restarted at 1 dose level lower. • If the nonhematological toxicity event recurs at ≥ Grade 3 at the lowest dose level available for the attributed study drug, the patient will be discontinued from that study treatment.
Grade ≥ 3 atrial fibrillation or hypertension	• For Grade ≥ 3 atrial fibrillation or hypertension that is not adequately controlled with oral medication, withhold study drugs. • For Grade ≥ 3 atrial fibrillation or hypertension that is adequately controlled with oral medication, study drug does not need to be held/reduced. • For patients experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: Following discussion with the study medical monitor, after the atrial fibrillation is adequately controlled study drug may be restarted at either the original dose or 1 dose level lower.
TLS	See Appendix 15.

Table 7: Venetoclax Dose Reduction Steps

Dose at interruption	Restart dose
400 mg	300 mg
300 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	20 mg
20 mg	10 mg

Table 8: Zanubrutinib Dose Reduction Steps

Dose Level	Zanubrutinib Dose
0 = starting dose	160 mg twice a day
-1 dose level	80 mg twice a day
-2 dose level	80 mg once a day

7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients will not have received prior systemic therapy for CLL/SLL with the exception of a prior aborted regimen of duration < 2 weeks.

7.2. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information and dates of administration.

TLS has been infrequently reported with zanubrutinib and ibrutinib treatment (particularly in patients who were treated for CLL). Patients with high tumor burden should be monitored closely and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards. For Cohort 3 (Arm D), TLS prophylaxis and management is discussed in Section 6.2.3.1 , Section 6.2.3.2, Section 6.2.3.3, and Appendix 15.

Prophylactic measures against infection (eg, for the prevention of bacterial, viral or fungal infections) and/or for the prevention of hepatitis B infection reactivation, may be used per institutional standards.

Patients with hematologic malignancies are predisposed to opportunistic infections as a result of a number of disease-related factors including immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow. In patients with a high risk of opportunistic infections, including Pneumocystis jirovecii pneumonia, prophylaxis should be considered as per institutional standards.

7.2.1. Permitted Medications

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-CLL/SLL indications
- Patients should not receive treatment with systemic corticosteroids other than intermittently to control or prevent infusion reactions, or for short durations (< 2 weeks) to treat non-CLL/SLL-related conditions (eg, to treat a flare of chronic obstructive pulmonary disease). Patients temporarily requiring systemic corticosteroids for longer durations (eg, to treat patients with coronavirus disease [COVID-19] who require oxygen support) should consult the medical monitor. Long-term chronic systemic corticosteroid use is not permitted, except for adrenal replacement – consult the medical monitor for this situation.
- Therapy to reduce symptoms per standard of care and institutional guidelines

For a patient in the treatment phase of the study who has a second primary malignancy, the investigator should obtain the medical monitor's approval before initiating any non-surgical treatment that is given concurrently with study drug.

Adjuvant antihormonal therapy for prostate or breast cancer is allowed. All localized treatments (such as radiation or surgery) expected to be completed within 6 weeks are allowed, provided the study drug is held during the period of localized anti-cancer treatment. Patients with a metastatic second primary malignancy who require systemic chemotherapy or immunotherapy must permanently discontinue study drug prior to start of the non-CLL/SLL cancer treatment. Patients who require therapy that may interact with study drug or significantly obscure the interpretation of CLL/SLL response should permanently discontinue study drug.

Permission from the medical monitor is required prior to restarting study drug after dose hold due to treatment for second primary malignancy.

7.2.2. Prohibited Medications

Patients should not receive other anticancer therapy for CLL/SLL (cytotoxic, biologic, or immunotherapy) while on treatment in this study. Other anticancer therapy for CLL/SLL should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the study drug.

7.2.2.1. For Arm D Only

Use of warfarin or warfarin derivatives is prohibited for patients in Arm D. Concomitant use of strong CYP3A inhibitors is not allowed for patients in Arm D during initiation of venetoclax and during the ramp-up phase.

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

7.3.1. CYP-Inhibiting/Inducing Drugs for Zanubrutinib

Clinical drug-drug interaction study with zanubrutinib showed that co-administration of zanubrutinib with the strong CYP3A inducer rifampin decreased $AUC_{0-\infty}$ of zanubrutinib by 13.5-fold in healthy subjects. Co-administration of zanubrutinib with strong CYP3A inhibitor itraconazole increased $AUC_{0-\infty}$ of zanubrutinib by 3.8-fold (refer to Section 1.3.2.2). These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 5 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib (Section 1.3). If all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and should consider using alternative agents. If these agents will be used, follow the dose modification table in Table 9. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Table 9: Dose Modification Table for Zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort) and moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use

Clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.3.2.2). Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Because ethinylestradiol (a key ingredient in a variety of combined oral contraceptives) is partly metabolized by CYP3A4, patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well (see Section 4.1). The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

7.3.2. Effect of Hepatic Impairment on the Pharmacokinetics of Zanubrutinib

No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for zanubrutinib adverse reactions in patients with hepatic impairment.

7.3.3. Warfarin for Venetoclax

Concomitant use of venetoclax increases warfarin exposure (based on C_{max} and AUC), which may increase the risk of bleeding. Use of warfarin or warfarin derivatives is prohibited for patients in Arm D.

7.3.4. Cytochrome P450 3A Inhibitors/Inducers and P-glycoprotein Inhibitors/Substrates for Venetoclax

Avoid concomitant use of venetoclax with moderate CYP3A inhibitors, strong or moderate CYP3A inducers (refer to Appendix 5 for a list of these medications), P-gp inhibitors, or narrow therapeutic index P-gp substrates. Refer to the current venetoclax label (VENCLEXTA USPI, Nov 2018; Venclyxto SmPC, May 2018).

- If a moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) or a P-gp inhibitor (eg, amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) must be used, reduce the venetoclax dose by at least 50%.
- If a strong CYP3A inhibitor must be used after the ramp-up phase, reduce the venetoclax dose by at least 75%.
- If a narrow therapeutic index P-gp substrate (e.g., digoxin, everolimus, and sirolimus) must be used, it should be taken at least 6 hours before venetoclax.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Adverse Events

8.1.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In these instances, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

8.1.1.1. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. When applicable, nonhematologic AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03; hematological toxicities will be graded based on the Grading Scale for Hematologic Toxicity in CLL Studies (see Appendix 9). For Arm D only, TLS will be graded per the Cairo-Bishop criteria (Appendix 16).

Nonhematologic toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.2.

Patients with CLL may have low blood counts at initiation of therapy. Lab abnormalities are only to be recorded as AEs if they have a clinical significance. Assessment of AE severity for clinically significant laboratory assessments (see Section 8.1.2) should be based on the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 9).

8.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Prescribing Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to the submission by email/fax of the SAE report to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related". An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered 'related' to study drug if any of the following are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.1.1.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. Any changes in the severity of AEs/SAEs must be recorded in the appropriate AE or SAE eCRF page(s); both increases in grade and decreases in grade will be recorded with updated start and stop dates. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report and eCRF, with all changes signed and dated by the investigator. The updated SAE report should be presented to the sponsor within the timeframes outlined in Section 8.5.1.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation) or other abnormal assessments (ECGs, X-rays, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worsen will not be reported as AEs or SAEs. The definition of clinically significant is left to the judgment of the investigator;

in general, these are events that result in clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation.

For anemia, neutropenia or thrombocytopenia, refer to the Grading Scale for Hematologic Toxicity in CLL Studies (see Appendix 9).

Asymptomatic treatment-related lymphocytosis should not be considered an AE.

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C, see Section 5.9.

8.1.3. Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

8.2. Serious Adverse Events

8.2.1. Definitions

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- NOTE: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE; it does not refer to an AE, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
- NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity
- NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure.

8.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported. If patients screen fail, reporting of SAEs will end at the time of screen failure. After initiation of study drug all AEs and SAEs regardless of relationship to study drug will be reported until end date as defined below.

For patients receiving zanubrutinib or zanubrutinib plus venetoclax, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until disease progression, whichever occurs later. In some cases, a patient may start another CLL/SLL therapy prior to disease progression. In such cases, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until the first day of the new CLL/SLL treatment, whichever is later.

For patients receiving B+R: all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or until date of confirmed disease progression, whichever occurs later. In some cases, a patient may start another CLL/SLL therapy prior to disease progression. In such cases, all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or until the first day of the new CLL/SLL treatment, whichever is later.

After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. Adverse events starting during the above defined reporting period but worsening to Grade 5 afterwards should also be reported.

Any new second primary malignancy, regardless of severity and relationship to study drug, should be reported until the end of the study.

8.4.2. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.4.3. Disease Progression

Disease progression is expected in this study population, and the term "disease progression" should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE term(s). For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion due to disease progression" instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure due to disease progression" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression". Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data.

If there is any uncertainty regarding whether an AE is due to disease progression, it should be reported as an AE.

The date of the first test result confirming disease progression will be used as the date of disease progression.

8.4.4. Death

Death is an outcome and not usually considered an event. If the only information available is death, the cause of death is unknown, and the death occurred within 30 days after the last dose of zanubrutinib, rituximab, or venetoclax or within 90 days after the last dose of bendamustine, then the death is reported as an event (eg, "death of unknown cause" or "death unexplained").

8.5. Prompt Reporting of Serious Adverse Events

8.5.1. Timeframes for Submitting Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 10.

Table 10: Timeframes and Documentation for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form

Abbreviations: AE, adverse event; SAE, serious adverse event.

8.5.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor via email within 24 hours as outlined in Section 8.5.1. The SAE report form will always be completed as thoroughly as possible with all available details of the SAE, signed or e-signed by the investigator (or designee), and forwarded to the sponsor within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.1.1.2.

The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

8.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the timelines detailed in Section 8.5.1 procedures in Section 8.5.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

All SUSARs (as defined in Section 8.3), will be submitted to all applicable regulatory authorities and investigators for zanubrutinib studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 90 days of the last dose of zanubrutinib, or within 12 months after the last dose of rituximab, or within 6 months (partner of male patient) or 3 months (female patient) after the last dose of bendamustine, whichever comes last, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an adverse event or serious adverse event.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as a SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as a SAE.

8.7. Post-Study Adverse Event

A post-study AE or SAE is defined as any AE that occurs after the AE/SAE reporting period, defined in Section 8.4.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

8.8. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs and IECs based on applicable legislation.

To determine the reporting requirements for individual serious adverse events, the sponsor will assess the expectedness of the SAEs using the following reference safety information (RSI) documents:

- Zanubrutinib Investigator's Brochure
- Bendamustine Prescribing Information
- Rituximab Prescribing Information
- Venetoclax Prescribing Information

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released.

Details of the statistical analyses will be included in a separate statistical analysis plan.

9.1. Study Endpoints

9.1.1. Primary Endpoint

The primary endpoint is progression-free survival in Cohort 1 (patients without del17p) determined by independent central review using the iwCLL guidelines with modification for treatment-related lymphocytosis in patients with CLL and the Revised Criteria for Response for Malignant Lymphoma in patients with SLL, and defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first.

9.1.2. Secondary Endpoints

- Overall response rate in Cohort 1 defined as the proportion of patients who achieve a complete response, complete response with incomplete bone marrow recovery, partial response, or partial response with lymphocytosis, determined by independent central review and by investigator assessment
- Overall survival in Cohort 1 defined as the time from randomization to the date of death due to any reason
- Duration of response in Cohort 1 determined by independent central review and by investigator assessment, using the iwCLL criteria with modification for treatment related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL), and defined as the time from the date that criteria for response (ie, PRL or better) are first met to the date that disease progression is objectively documented or death, whichever occurs first
- Progression-free survival in Cohort 1 determined by investigator assessment
- Patient-reported outcomes in Cohort 1 measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Progression-free survival in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment
- Overall response rate in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment
- Duration of response in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment
- Overall response rate in Cohort 2 (patients with del17p), Arm C, determined by independent central review and investigator review

- Progression-free survival in Cohort 2 (Arm C), determined by independent central review and investigator review
- Duration of response in Cohort 2 (Arm C), determined by independent central review and investigator review
- Overall response rate in Cohort 3 (patients with del17p or pathogenic TP53 variant), Arm D, determined by investigator review
- Progression-free survival in Cohort 3 (Arm D), determined by investigator review
- Duration of response in Cohort 3 (Arm D), determined by investigator review
- Cohort 3 (Arm D) only: undetectable MRD4 rate
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical examinations, and vital signs
- Pharmacokinetic parameters of zanubrutinib such as apparent clearance of the drug from plasma (CL/F) and AUC from time 0 to 12 hours postdose (AUC_{0-12}) for Arms A, C, and D

9.1.3. Exploratory Endpoints

- Progression-free survival 2 (PFS2) for Arms A, B, and C, determined by investigator assessment, defined as the time from randomization to the date of progression on the next line of therapy subsequent to the study treatment.
- Clinical outcomes (eg, progression-free survival, overall response rate, duration of response, overall survival) correlated with baseline prognostic and predictive markers (eg, deletion 11q22-23, mutation status of IGHV, pathogenic TP53 variant, β-2 microglobulin level, deletion 13q14, trisomy 12)
- Overall survival in pooled Cohort 1/1a patients from Chinese sites
- Patient-reported outcomes in pooled Cohort 1/1a patients from Chinese sites
- Overall survival in Cohort 2 (Arm C)
- Patient-reported outcomes in Cohort 2 (Arm C), measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Overall survival in Cohort 3 (Arm D)
- Patient-reported outcomes in Cohort 3 (Arm D), measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax in Cohort 3
- Medical resource utilization in Cohort 1/1a as assessed by the number of hospitalizations, length of hospital stay, and supportive care in patients
- Medical resource utilization in Cohort 2 as assessed by the number of hospitalizations, length of hospital stay, and supportive care in patients

- Medical resource utilization in Cohort 3 as assessed by the number of hospitalizations, length of hospital stay, and supportive care in patients
- Pharmacokinetic parameters of venetoclax such as apparent clearance of the drug from plasma (CL/F) and AUC from time 0 to 12 hours postdose (AUC_{0-12}) for Arm D

9.2. Statistical Analysis

All inferential statistics described in this section refer to the efficacy comparisons of Arms A and B in Cohort 1. Efficacy results of Arms A and B will also be compared in patients from Chinese sites enrolled in Cohort 1/1a for the endpoints defined for the Analysis Set for Patients from Chinese Sites. Separate summary statistics in Cohorts 2 and 3 will be used to report the efficacy and safety of zanubrutinib by each arm.

9.2.1. Randomization Methods

As discussed in Section 5.2, patients will be randomized using the IRT system for this study by permuted block stratified randomization.

The stratified randomization will be produced, reviewed, and approved by an independent statistician.

9.2.2. Analysis Sets

The Intent-to-Treat (ITT) Analysis Set includes all enrolled patients who are assigned to a treatment group by the IRT system. The ITT Analysis Set will be the primary population for Cohort 1 efficacy analyses.

The Safety Analysis Set includes all patients who received any dose of study drug. Patients will be included in the treatment group corresponding to the actual treatment received. The Safety Analysis Set will be used for all safety analyses.

The Per-Protocol Analysis Set includes patients who received any dose of study medication and had no important protocol deviations. Criteria for exclusion from the Per-Protocol Analysis Set will be determined and documented before the database lock for the primary analysis.

The PK Analysis Set includes all zanubrutinib-treated patients for whom valid zanubrutinib PK parameters can be estimated.

The Analysis Set for Patients from Chinese Sites includes all patients from Chinese sites enrolled in Cohort 1/1a and randomized to a treatment group by the IRT system.

9.2.3. Efficacy Analysis

9.2.3.1. Primary Efficacy Endpoint Analysis

Primary inference of comparing PFS assessed by independent central review between the 2 arms in Cohort 1 will be based on log-rank test stratified by randomization stratification factors (age [$<$ 65 years vs $\geq$ 65 years], Binet stage [C vs A or B], and IGHV mutational status [mutated vs unmutated) in the ITT Analysis Set.

The null and alternative hypotheses for testing PFS superiority of Arm A to Arm B in Cohort 1 are as follows:

H_0: Hazard ratio (HR) (Arm A/Arm B) = 1

H_a: HR (Arm A/Arm B) = 0.58

The HR and its 2-sided 95% confidence interval (CI) will be estimated from a stratified Cox regression model. The distribution of PFS, including median PFS and PFS rate at selected timepoints such as 12 and 24 months, will be estimated using the Kaplan-Meier method for each arm.

The censoring rules for PFS in the primary analysis will follow FDA Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (2018) as follows.

- PFS for patients without any post-baseline tumor assessment will be censored at the time of randomization
- PFS for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment
- PFS for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date
- PFS for patients who start to receive new CLL/SLL anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy
- PFS for patients with disease progression or death occurring immediately after two or more missed consecutive disease assessments will be censored at the last tumor assessment before the missed consecutive disease assessments

Alternative censoring rules, such as not censoring PFS due to receipt of new anticancer therapy for CLL/SLL, will be used in sensitivity analyses of PFS. Another sensitivity analysis of PFS will be based on all patients randomized to Cohort 1 and Cohort 1a. Additional details will be provided in the SAP.

9.2.3.2. Secondary Efficacy Endpoint Analyses

Overall Response Rate

ORR will be calculated for each treatment group with Clopper-Pearson 95% CI. The odds ratio in ORR will be calculated along with its 2-sided 95% CI using the stratified Cochran-Mantel-Haenszel method. Given the high level of ORR (95%) observed in the B+R arm patients in the CLL10 study (Eichhorst et al 2016b), the comparison between treatment groups for the ORR endpoint in Cohort 1 will be descriptive.

Best overall response is defined as the best response recorded from randomization until data cut or start of new CLL/SLL anticancer treatment. Patients with no post-baseline response assessment (due to any reason) will be considered as nonresponders. The proportion of each of the best response categories (CR, CRi, PR, nodular partial response, partial response with lymphocytosis, SD, and progressive disease) will be also presented by treatment group.

Overall Survival

Primary inference of comparing OS between the 2 arms in Cohort 1 will be based on a log-rank test stratified by the randomization stratification factors age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated) in the ITT Analysis Set.

The HR and its 95% CI will be computed from a stratified Cox regression model. Distribution of OS including median and OS rate at selected time-points, will be summarized using the Kaplan-Meier method for each arm.

Duration of Response

Distribution of duration of response will be summarized using the Kaplan-Meier method for each arm. Hypothesis testing comparing duration of response between the 2 arms will not be performed.

Progression-Free Survival by Investigator Assessment

PFS will be calculated based on investigator-assessed tumor responses. PFS by investigator assessment will be analyzed using the same methods as the primary endpoint of PFS by independent central review.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint. The percentage of patients with a clinically meaningful change from baseline in 'global health status/QOL' and functional domains will be summarized as "improved", "stable" or "worsened" and compared between Arms A and B. The scale will be compared between treatment groups using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) to account for missing data under Missing at Random (MAR) assumption (Mallinckrodt et al 2008). The analysis will be based on the ITT population. The dependent variable of this model will be the QLQ-C30 Global Health Status/QoL score measured along with disease assessments at baseline, Week 12, and Week 24. The model will include treatment, time, as well as the three randomization stratification factors as fixed effects. The random patient effects will include patient random intercept on QLQ-C30 Global Health Status/QoL score. The subject random effects are assumed to follow a normal distribution. A point estimate of the treatment difference between the BGB-3111 and B+R arms, the corresponding p-value, and the 95% confidence interval will be provided and used as the primary inference for the QLQ-C30 Global Health Status/QoL endpoint.

Change of EQ-5D-5L score will be summarized descriptively.

Analysis in the Analysis Set for Patients from Chinese Sites

PFS by independent central review and by investigator assessment will be summarized for Arms A and B in the Analysis Set for Patients from Chinese Sites. PFS HR between the 2 arms and its 2-sided 95% CI will be estimated from a stratified Cox regression model using randomization stratification factors (age [< 65 years versus ≥ 65 years], Binet stage [C vs A or B], and IGHV mutational status [mutated vs unmutated) in the Analysis Set for Patients from Chinese Sites. The PFS results per independent central review between patients from Chinese sites and global patients will be in the same direction if both the estimated PFS HRs in the Analysis Set for

Patients from Chinese Sites and Cohort 1 patients are < 1 given PFS HR based on the ITT Analysis Set crosses the prespecified statistical boundary).

ORR and duration of response will be summarized for each treatment group.

Cohort 2

PFS, ORR, and duration of response of Cohort 2 (Arm C) will be summarized descriptively. Independent central review data as well as investigator assessed response data will be used for PFS, ORR and duration of response. The Kaplan-Meier method will be used to summarize the distribution of PFS and duration of response including quartiles and event-free rates at selected timepoints. An estimate of ORR with 95% Clopper-Pearson CI will be generated.

Cohort 3

PFS, ORR, and duration of response of Cohort 3 (Arm D) will be summarized descriptively. Investigator-assessed response data will be used for PFS, ORR and duration of response. The Kaplan-Meier method will be used to summarize the distribution of PFS and duration of response including quartiles and event-free rates at selected timepoints. An estimate of ORR with 95% Clopper-Pearson CI will be generated. Undetectable MRD4 rate will be estimated as the crude proportion of patients in Arm D who archive undetectable MRD4. Associated 95% Clopper-Pearson CI will be provided.

9.2.3.3. Exploratory Efficacy Analyses

OS of Cohort 2 (Arm C) and Cohort 3 (Arm D) will be summarized (separately) using descriptive statistics. The Kaplan-Meier method will be used to summarize OS including quartiles and event free rates at selected timepoints. OS for the Analysis Set for Patients from Chinese Sites will be analyzed using the same methods as described in the "Overall Survival" section.

PFS2 will be analyzed using the same methods used for other time to event endpoints such as PFS or OS. PFS2 will be compared between the 2 treatment groups.

Cox and/or logistic regression models, as well as descriptive comparisons, may be used to explore the association between prognostic and predictive biomarkers and clinical outcomes.

Patient-reported outcomes for the Analysis Set for Patients from Chinese Sites will be analyzed using the same method as described in the "Patient-Reported Outcomes" section.
Patient-reported outcomes for Cohort 2 will be summarized descriptively. Patient-reported outcomes for Cohort 3 will be summarized descriptively.

Medical resource utilization will be summarized at each visit (including screening and the first dose date) for each cohort, including the number of hospitalizations, length of hospital stay, and supportive care.

For Cohort 3 (Arm D) patients who discontinue either venetoclax or zanubrutinib or both due to achievement of complete response/undetectable minimum residual disease (CR/uMRD), patient time-to-recurrence of detectable minimum residual disease after discontinuation will be summarized descriptively using the Kaplan-Meier method.

9.2.3.4. Sensitivity Analysis

Cohort 1: For the primary endpoint of PFS by independent central review, alternative censoring rules such as not censoring for new CLL/SLL anticancer therapy will be used and the primary analysis as described in Section 9.2.3.1 will be repeated as a sensitivity analysis. PFS by independent central review will be analyzed using the Per-Protocol Analysis Set as well. The validity of proportional hazard assumption in the primary PFS analysis will be assessed, and an alternative analysis under a non-proportional hazard assumption will be performed if the validity of a proportional hazard assumption is rejected.

A subgroup analysis for PFS by independent central review and selected secondary endpoints will be performed.

Analysis of PFS per independent central review will be repeated using all patients randomized to Cohort 1 and Cohort 1a as a sensitivity analysis.

9.2.4. Pharmacokinetic Analyses

Plasma zanubrutinib concentrations will be summarized by scheduled time of collection. A population PK analysis may be performed to include plasma concentrations of zanubrutinib from this trial in an existing model. PK parameters such as CL/F and $AUC_{0\text{-}12}$ may be derived from the population PK analysis if supported by data.

An exposure-response (efficacy or safety endpoints) analysis may be performed if supported by data. The results from the population PK and exposure-response analyses may be reported separately from the Clinical Study Report (CSR).

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03 or based on the Grading Scale for Hematologic Toxicity in CLL Studies (see Appendix 9), as applicable. For Arm D only, TLS will be graded per the Cairo-Bishop criteria (Appendix 16). Laboratory values (CBC, serum chemistry and coagulation), vital signs, physical examinations and ECG findings will also be used in assessing safety. Descriptive statistics will be used to analyze all safety data by treatment group, as well as by combining Arms A and C in the Safety Analysis Set. Safety will be summarized separately for Arm D. Safety analysis will also be performed by treatment group for all patients from Chinese sites enrolled in Cohort 1/1a in the Safety Analysis Set.

9.3.1. Extent of Exposure

Extent of exposure to study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity (%).

The number (and percentage) of patients with dose reductions, dose interruption, dose delay, and drug discontinuation will be summarized with the respective reasons. The cycles in which dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of dose modifications will be summarized by categories.

Patient data listings will be provided for all dosing records and for calculated summary statistics.

9.3.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 20.0 or higher) lowest level term closest to the verbatim term.

A treatment-emergent AE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days for Arm A, C, and D patients and 90 days for Arm B patients following study drug discontinuation or the start of new anticancer therapy for CLL/SLL, whichever comes first. Worsening of a TEAE to Grade 5 beyond 30 days after the last dose of zanubrutinib or venetoclax, or beyond 90 days after the last dose of rituximab or bendamustine, is also considered a TEAE. Two sets of summary tables will be provided: TEAEs and TEAEs plus AEs/SAEs reported during the Post-treatment Follow-up phase. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAE plus post-treatment phase AEs will be reported as the number (and percentage) of patients with TEAEs plus post-treatment phase AEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade according to CTCAE v4.03 within a system organ class and preferred term, even if the patient experienced more than 1 TEAEs or post-treatment phase AEs within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs plus post-treatment phase AEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs plus post-treatment phase AEs ≥ Grade 3, study drug-related TEAEs plus post-treatment phase AEs and treatment-emergent AEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Incidence and time to diarrhea (≥ Grade 3), severe bleeding (defined as ≥ Grade 3 bleeding of any site or central nervous system bleeding of any grade), and atrial fibrillation (both new onset and exacerbation of existing atrial fibrillation) will also be summarized.

9.3.3. Laboratory Analyses

CBC and serum chemistry values will be evaluated for each laboratory parameter by treatment group. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI-CTCAE (v4.03) will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately. The incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia), which are graded based on the Grading

Scale for Hematologic Toxicity in CLL Studies (Appendix 9), and Grade 3 and 4 TLS, which is graded per the Cairo-Bishop criteria (Arm D only; Appendix 16), will also be provided.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, and weight) and changes from baseline will be presented by visit and treatment group for all visits. Vital signs will be listed by patient and visit.

9.3.5. Electrocardiogram

ECG assessments will be performed at the screening visit. Descriptive statistics for baseline ECG parameters will be presented.

9.4. Sample Size Consideration

The sample size calculation for Cohort 1 is based on the primary efficacy analysis of PFS by independent central review which compares Arms A and B in Cohort 1. Assuming the PFS HR (Arm A/Arm B) in Cohort 1 is 0.58, 118 events are required to achieve 83.5% power at 2-sided alpha of 0.05 to reject the null hypothesis when 1 interim analysis is planned after 73% of the target number of events at final analysis. If 450 patients are enrolled to Cohort 1 and randomized in a 1:1 ratio to Arms A and B over a 25-month period (actual patient enrollment up to November 2018 and 28 patients per month enrollment rate after) and the hazard rate for drop-out of 0.0017/month, 118 PFS events are expected to be accumulated at 41 months from study start. This assumes a median PFS in Arm B of 42 months and that PFS follows exponential distribution. The details of progression-free survival interim and final analyses are described in the Primary Efficacy Analysis section (Section 9.2.3.1). Approximately 710 patients will be enrolled, with 450 patients without the del17p mutation in Cohort 1 available for the primary efficacy analysis, approximately 80 additional patients from Chinese sites without the del17p mutation in Cohort 1a, approximately 100 patients with the del17p mutation in Cohort 2, and approximately 80 patients with the del17p mutation in Cohort 3. For patients in Cohort 3 with a central FISH test result other than del17p-positive CLL/SLL, those with a local laboratory test result documenting pathogenic TP53 variant may be eligible for enrollment.

Sample size selection for Cohort 1a was to accumulate enough PFS events among patients enrolled from Chinese sites to support more than 80% probability of demonstrating an HR < 1 among patients enrolled from Chinese sites at the final analysis if the PFS HR based on the ITT Analysis Set crosses the prespecified statistical boundary at the final analysis. Sample size selections for Cohorts 2 and 3 were driven by estimated patient availability.

9.5. Interim Analysis

There will be 1 interim analysis of PFS by independent central review in Cohort 1. O'Brien-Fleming boundary approximated by Lan-DeMets spending function will be implemented for both efficacy and futility. The interim analysis will be performed when approximately 86 events (73% of the target number of events at final analysis) from Arms A and B in Cohort 1 are observed. It is estimated that it will take approximately 33 months to observe 86 events under the assumptions described in Section 9.4. The futility will be non-binding.

9.6. Final Analysis

The final analysis of PFS will take place after 118 events are observed in Cohort 1, which is estimated as approximately 41 months from study start. Stopping boundaries for futility and efficacy at the interim and final analyses are shown in Table 11. The boundaries will be adjusted based on actual number of events observed at the interim analysis. Nominal p-value boundary will be used for primary inference at both interim and final analyses.

Table 11: Stopping Boundaries for Interim and Final Analyses of Progression-Free Survival

	Time (months)	# PFS events	Nominal p-value (Z score) for efficacy	Nominal p-value (Z score) for interim futility
Interim analysis	33	86	< 0.009 (> 2.38)	> 0.313 (< 0.489)
Final analysis	41	118	< 0.022 (> 2.007)	-

Abbreviations: HR, hazard ratio; PFS, progression-free survival.

If the efficacy boundary is met and the DMC recommends stopping the study for efficacy, the sponsor may stop Cohort 1 and file the results to regulatory agencies for approval. If Cohort 1 stops at the interim analysis, patients from Chinese sites will be followed until 10 PFS events are accumulated and the PFS analysis in the Analysis Set for Patients from Chinese sites will be performed at that time. If Cohort 1 stops at the final analysis, the final analysis of PFS for the Analysis Set for Patients from Chinese Sites will be performed concurrently.

The final analysis of OS will be performed at the end of the study, approximately 5 years after the first patient is randomized. Two interim analyses of OS are planned at the time of the interim and final analysis of PFS. Given a 3-year, 92% survival rate observed in patients in the B+R arm in the CLL10 study (Eichhorst et al 2016a), the planned interim OS analyses are not expected to have enough power to show statistical difference between the two arms. Therefore, a one-sided 0.00005 alpha will be set for each of the two planned interim analyses.

9.7. Other Statistical Issues

9.7.1. Multiplicity Adjustment

The multiplicity due to testing of multiple hypotheses for primary endpoint (PFS by independent central review) is adjusted by O'Brien Fleming type Lan-DeMets alpha spending function as described in Section 9.5.

9.7.2. Secondary Endpoint Testing Procedures

For Cohort 1, the secondary endpoints, OS and PRO, will only be tested if the primary endpoint, PFS, is significant. No inferential testing will be done for other secondary endpoints including ORR and DOR.

The multiplicity in testing the OS and PRO secondary endpoints will be adjusted per fixed sequencing Bonferroni (FSB) method (Wiens, 2003). Unlike the regular fixed sequencing method in which the endpoints in the later order are tested only when all the higher ranked endpoints are statistically significant, this method allows the lower ranked endpoints to be tested

even when the higher ranked ones are not statistically significant. The 0.025 significance level is initially evenly distributed to the two endpoints. If one of them is positive at the 0.0125 significance level, then the other endpoint will inherit the significance level and be tested at 0.025. For example, at the primary PFS analysis time, if PRO has the smaller p-value and it is less than 0.0125, then OS will be tested at 0.025. The significance level for the PRO analysis will be α_{pro}, irrespective of whether the test is performed at the interim or final PFS analysis time, because PRO data will be mature (last patient dosed + 6 treatment cycles) before the interim PFS analysis. The significance level for the OS analysis at the interim and final PFS analysis will be 0.00005 and the final OS analysis will be assigned a one-sided alpha of α_{os}-0.0001. Both α_{pro} and α_{os} will be determined by the FSB procedure described above at the time of primary PFS analysis. The proposed testing procedure is equivalent to the graphical approach-based testing described by Maurer and Bretz (Maurer and Bretz, 2013).

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Steering Committee

This study will be overseen by a Steering Committee consisting of experts in CLL/SLL and members of the sponsor's staff. The Steering Committee plays a central role in the design of the study, oversees the conduct of the study, and is to agree on a plan for communication of the results.

10.2. Data Monitoring Committee

An independent data monitoring committee (DMC) consisting of experts in CLL/SLL, clinical trial safety monitoring, and statistics will evaluate safety data on a periodic basis and perform the efficacy interim analysis for this study. Approximately every 6 months, the DMC will review all available safety data. In addition to the regular DMC meetings, the DMC will review data from approximately the first 6 patients in Arm D who complete at least 1 cycle of venetoclax. A separate charter will outline the details for the composition and responsibility of the DMC.

10.3. Independent Central Review

The sponsor will contract with an independent central review facility to provide an independent and blinded review of imaging and clinical data necessary to assess tumor response in the BGB-3111-304 study. This may include request for standard of care non-protocol imaging, if applicable. The independent central review will be conducted by qualified, board-certified radiologists and hematologists assigned to the BGB-3111-304. An independent central review charter will describe the independent review and define the processes, roles, and responsibilities of the sponsor, the sites, the independent central review facility, and the reviewers.

10.4. Provision of Study Results and Information to Investigators

When the CSR is completed, the sponsor will provide the major findings of the study to the investigator.

In addition, details of the study drug assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

The sponsor will not routinely inform the investigator or patient the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to appropriate regulatory agency before the study is initiated at a study center in that country.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Conference on Harmonisation guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

11.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new patients can consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.5.3, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent form process, either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator must assure that patients' confidentiality will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (ie, not names) and date of birth or year of birth (depending on local regulations) may be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, CRFs, the investigational drug, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.2.6. Case Report Forms

For each patient randomized/assigned to treatment, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. If a patient withdraws from the study, the reason must be noted in the appropriate eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRF exists within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system.

Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRF is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data from that site (eg, paper, CD, or other appropriate media) for archiving the data at the study site.

11.2.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.2.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.9. Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

11.2.10. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interests of clinical investigators and/or disclose those financial interests, as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

11.3. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and /or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

11.4. Study Report and Publications

A CSR will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Conference on Harmonisation Guideline for Structure and Content of Clinical Study Reports (International Conference on Harmonisation E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2013).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor before submission or presentation. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay in publication/presentation may be requested by the sponsor to allow for patent filings in advance of publication/presentation.

11.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

11.6. Records Retention and Study Files

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples remaining after this study may be retained in storage by the sponsor for a period up to 10 years.

11.7. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose to provide appropriate medical care to a patient
- Study results which may be published as described in Section 11.4.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

11.8. Joint Investigator/Sponsor Responsibilities

11.8.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.8.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

PROTOCOL NO: BGB-3111-304

This protocol is a confidential communication of BeiGene, Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd.

Instructions to the Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2. CLL RESPONSE DEFINITIONS

(From Modified IWCLL guidelines Hallek et al 2008 and Cheson et al 2012)

Parameter	Complete Response[e]	Partial Response[g]	Partial Response with Lymphocytosis[i]	Progressive Disease[j]
Group A				
Lymphadenopathy[a]	None > 1.5 cm	Decrease ≥ 50% from BL	Decrease ≥ 50% from BL	Increase ≥ 50% from nadir or new lesion
Hepatomegaly[b]	None	Decrease ≥ 50% from BL	Decrease ≥ 50% from BL	Increase ≥ 50% from nadir or new hepatomegaly when none at BL
Splenomegaly[c]	None	Decrease ≥ 50% from BL	Decrease ≥ 50% from BL	Increase ≥ 50% from nadir or new splenomegaly when none at BL
Blood lymphocytes	< 4000/µL	< 5000/µL OR decrease ≥ 50% from BL	Decrease < 50% or increase from BL	Progression based on increasing ALC alone Increase ≥ 50% from nadir and ALC ≥ 5000/µL[k]
Marrow[d]	< 30% lymphocytes and no B-lymphoid nodules. See footnote f for definition of CRi.	50% reduction in marrow infiltrate, or B-lymphoid nodules[h]	50% reduction in marrow infiltrate, or B-lymphoid nodules	Not Applicable
Group B				
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over BL	> 100,000/µL or increase ≥ 50% over BL	Decrease of ≥ 50% from BL secondary to CLL[l]
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over BL	> 11 g/dL or increase ≥ 50% over BL	Decrease of > 2 g/dL from BL secondary to CLL[l]
Neutrophils[d]	> 1500/µL	> 1,500/µL or increase > 50% over BL	> 1,500/µL or increase > 50% over BL	Not Applicable

Abbreviations: BL, baseline (The most recent data/value prior to first dose of study drug); CBC, complete blood count; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete hematopoietic recovery; CT, computed tomography; eCRF, electronic case report form; PR, partial response.
NOTE: A Best OR of CR, CRi, nPR, PR, or PR-L should be confirmed no earlier than 8 weeks from the time a response of CR, CRi, nPR, PR, or PR-L is first suspected (SD does not require confirmation). At a minimum, a physical exam and complete blood count with differential will be needed to confirm the Best OR.
NOTE: Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

a. For CR, all CLL-related lesions must resolve. For determination of other categories, the percent change is calculated from the sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination). NOTE: A single lymph node increase from nadir of ≥ 50% in the longest diameter, if unequivocal, will confirm disease progression. NOTE: Other clinical factors that could result in temporary lymphadenopathy (ie, infection) should be ruled out in order to confirm progression.
b. Percent change is relative to only the abnormally enlarged portion of the organ documented at baseline. No firmly established international consensus of the size of a normal liver is available (Hallek et al, 2018); therefore, liver size should be evaluated by imaging and manual palpation and the size of the abnormal portion is to be documented at baseline and subsequent post-baseline response evaluations. Disease progression requires a ≥ 50% increase in the abnormal portion from nadir (if an abnormal portion exists at nadir) and a minimum absolute increase in the abnormal portion by at least 2 cm. NOTE: Other clinical factors that could result in temporary hepatomegaly (ie, infection) should be ruled out in order to confirm progression. NOTE: If the liver is barely palpable but still considered enlarged on physical examination, enter "0.5 cm" as the measurement for "centimeters below right costal margin" on the corresponding eCRF page.
c. Normal spleen length is ≤13 cm. Percent change is relative to only the abnormally enlarged portion of the organ documented at baseline. For example, a patient with a total craniocaudal spleen length at baseline of 18 cm has a 5 cm abnormal spleen length: 18 cm – 13 cm (normal spleen size)= 5 cm abnormal portion. If the total length of the spleen at Week 12 is 15 cm, then the % change from baseline is 3/5= 60% decrease, which meets the splenomegaly "A" parameter definition for partial response. Disease progression requires a ≥ 50% increase in the abnormal portion from nadir (if an abnormal portion exists at nadir) and a minimum absolute increase in the abnormal portion by at least 2 cm. NOTE: Other clinical factors that could result in temporary splenomegaly (ie, infection) should be ruled out in order to confirm progression. NOTE: If the spleen is barely palpable but still considered enlarged on physical examination, enter "0.5 cm" as the measurement for "centimeters below left costal margin" on the corresponding eCRF page.
d. These parameters are irrelevant for some response categories.
e. CR - Complete response: All CLL-related lesions must resolve. In addition, all the criteria must be met, including CBC data confirming CR without need for exogenous growth factors within the prior 14 days, and patients must lack disease-related constitutional symptoms.
f. CRi - Complete response with incomplete hematopoietic recovery: all the criteria met for complete response except the patient has at least 1 peripheral blood cytopenia (anemia, thrombocytopenia, and/or neutropenia).
g. PR - Partial response: Only those Group A parameters which were previously abnormal at BL can be used to evaluate PR response. If 2 or more Group A parameters are abnormal at BL, then at least 2 of them must meet PR criteria. If only one Group A parameter is abnormal at BL, then that parameter must meet PR criteria. In both cases, at least 1 Group B parameter must also meet PR criteria.
h. nPR - Nodular partial response: all the criteria met for complete response except for the presence of lymphoid nodules in the bone marrow
i. PRL - Partial response with lymphocytosis: PR criteria are otherwise met while blood lymphocytes are only decreased < 50% from BL or are or increased from BL. NOTE: PRL may only be assessed for patients treated with zanubrutinib and would override disease progression by ALC alone only for patients on zanubrutinib. NOTE**:** BTK inhibition may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease.
j. PD - Progressive disease: at least 1 of the above progressive disease criteria must be met. Transformation to a more aggressive histology evidenced by biopsy is also considered as progressive disease.
k. For assessment of PD by ALC alone:
    - During treatment: the increase in ALC should be assessed against the baseline lymphocyte count and not cycle-by-cycle lymphocyte counts, which may not be stable.

- After treatment: the increase should be assessed against the lowest lymphocyte count assessed at the first follow-up visit after the end of 6 cycles of therapy.
- For patients who did not receive 6 cycles of treatment: compare ongoing ALC against the lowest lymphocyte count assessed starting from C7D1.

For assessment of PD by new lesion, one of the following criteria must be met:

- A new node > 1.50 cm in any axis
- A new extranodal site > 1.0 cm in any axis OR if ≤ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to CLL/SLL
- Assessable disease of any size unequivocally attributable to lymphoma

l. After treatment, the progression of peripheral cytopenia(s), as documented by a decrease of hemoglobin levels by > 20 g/L (2 g/dL) from baseline or to < 100 g/L (10 g/dL), or by a decrease of platelet counts by ≥ 50% from baseline or to < 100 x 10^9/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if the bone marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Other clinical factors that could result in the temporary appearance of a new lesion (ie, infection) should be ruled out in order to confirm progression.

SD - Stable disease: is absence of progressive disease and failure to achieve at least a PR or PRL.

For cases of Indeterminate response due to zanubrutinib dosing hold: see below.

Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly (defined as vertical spleen length > 13 cm) during periods of zanubrutinib hold will not be considered as progressive disease unless confirmed by a repeat imaging studies at least 6 weeks after restarting study drug administration. The response category “indeterminate due to zanubrutinib hold” should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

APPENDIX 3. MODIFIED LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

Response and Site	CT-Based Response (Patients Without PET-Avid Disease at Screening)*
Complete	Complete radiologic response (all of the following):
Lymph nodes and extralymphatic sites	• Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion • No extralymphatic sites of disease
Non-measured lesion	Absent
Organ enlargement	Regress to normal
New lesions	None
Bone marrow	Normal by morphology, if indeterminate, immunohistochemistry negative
Partial	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	• ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When no longer visible, 0 x 0 mm • For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Absent/normal, regressed, but no increase
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal
New lesions	None
Bone marrow	Not applicable
No response or stable disease	Stable disease
Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	No increase consistent with progression
Organ enlargement	No increase consistent with progression
New lesions	None
Bone marrow	Not applicable

Response and Site	CT-Based Response (Patients Without PET-Avid Disease at Screening)*
Progressive disease** Individual target nodes/nodal masses	Progressive disease requires at least 1 of the following cross product of the longest transverse diameter of a lesion and perpendicular diameter progression: An individual node/lesion must be abnormal with: • longest transverse diameter of a lesion > 1.5 cm and • Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and • An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Non-measured lesions	New or clear progression of pre-existing non-measured lesions
New lesions	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if ≤ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow***	New or recurrent involvement

Abbreviations: CT, computed tomography; FDG, [18F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
Modified from Cheson et al, 2014.
*Normal spleen length is ≤13 cm. NOTE: If the spleen is barely palpable but still considered enlarged on physical examination, enter "0.5 cm" as the measurement for "centimeters below left costal margin" on the corresponding eCRF page.
**Progressive disease must be confirmed by repeat imaging no sooner than 4 weeks from the first imaging that show possible progression to rule out pseudo-progression. Patients may continue study treatment while they wait for the confirmation imaging. An exception to the confirmatory scan requirement exists if one or more of the following clear, clinical signs of progression is present and the applicable reviewer believes the progression is unequivocal:

- Clinical symptoms and signs of disease progression (including worsening laboratory values, biopsy-proven disease transformation, etc.)

- Rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that, in the opinion of the reviewer, is unequivocal

***After treatment, the progression of peripheral cytopenia, as documented by a decrease of hemoglobin levels by > 20 g/L (2 g/dL) from baseline or to < 100 g/L (10 g/dL), or by a decrease of platelet counts by ≥ 50% from baseline or to < 100 x 10^9/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if the bone marrow biopsy demonstrates an infiltrate of SLL cells.

NOTE: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy, and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

BTK inhibition may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. The opposite may occur during periods of temporary holds of BTK inhibitors (due to adverse events or other reasons), and leukemia cells may redistribute from the blood to lymphoid tissue; this also is not a sign of treatment failure or progressive disease.

Isolated increase in lymph nodes and/or splenomegaly (defined as vertical spleen length > 13 cm) during periods of zanubrutinib hold will not be considered as progressive disease unless confirmed by a repeat imaging study at least 6 weeks after restarting study drug administration. The response category “indeterminate due to zanubrutinib hold” should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

APPENDIX 4. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX 5. CYP3A INHIBITORS AND INDUCERS

IMPORTANT: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

Examples of Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone, idelalisib
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Examples of Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice), Seville oranges
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Examples of Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Abbreviation: CYP: cytochrome P450.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. For a more complete list, please refer to the Flockhart Table: http://medicine.iupui.edu/clinpharm/ddis/main-table

APPENDIX 6. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 7. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

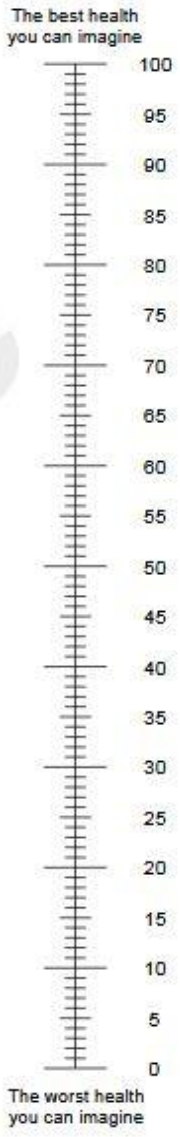
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



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APPENDIX 8. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 9. GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

Hematologic Grading Scheme

Grade[1]	Decrease in platelets[2] or Hgb[3] (nadir) from pretreatment value	Absolute neutrophil count/μL[4] (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

Abbreviation: HgB, hemoglobin.
Source: Hallek et al, 2008

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $< 20 \times 10^9$/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (Hgb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hgb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the ANC reaches $< 1 \times 10^9$/L (1000/μL), it should be judged to be Grade 3 toxicity. Other decreases in the WBC, or in circulating neutrophils, are not to be considered because a decrease in the WBC is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9$/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

APPENDIX 10. SCHEDULE OF ASSESSMENTS FOR ARMS A AND C (ZANUBRUTINIB)

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycle 2**	**Cycle3 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 96 weeks (approximately 24 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 4**	**± 14**	**± 14**	**± 14**
Informed consent, screen number[c]	X						
Medical and cancer history	X						
Eligibility authorization packet[d]	X						
Cohort and arm assignment[e]	X						
Zanubrutinib dispensing and accountability[f]		X	X	X	X		
Sparse PK sampling[g]		X	X				
Safety Assessments							
Echocardiogram[h]	X						
Vital signs (temperature, BP, heart rate)	X	X	X	X	X		
Physical examination[i]	X	X	X	X	X		
ECOG performance status	X	X	X	X	X		
12-Lead ECG (local read)[j]	X						
Concomitant medications review	X	X	X	X	X		
AE review[k]		X	X	X	X		X

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycle 2**	**Cycle3 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 96 weeks (approximately 24 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 4**	**± 14**	**± 14**	**± 14**
Safety Follow-up Visit[l]		X					
Efficacy Assessments							
Disease-related constitutional symptoms	X					X	
Physical examination of liver, spleen and lymph nodes[m]	X					X	
CT with IV and oral contrast[n]	X					X	
Bone marrow examination[o]	X					X	
PRO questionnaires[p]		X				X	
Overall response assessment						X	
Survival status and new anticancer therapy							X
Laboratory Assessments							
Hematology[q], chemistry[r,s]	X	X	X	X	X	X	
Serum immunoglobulins[t]	X			X	X		
Coagulation[u]	X						
del17p (FISH), cytogenetics[v]	X						
Peripheral blood flow cytometry for MRD[w]	X					X	

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycle 2**	**Cycle3 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 96 weeks (approximately 24 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 4**	**± 14**	**± 14**	**± 14**
Peripheral blood for IGHV mutation analysis[x]	X						
Peripheral blood for molecular markers of disease sample[y]	X					X	
Peripheral blood for mechanisms of resistance biomarker sample[z]						X	
Hepatitis B and C testing[aa]	X						
Pregnancy test (if applicable)[bb]	X within 7 days before random-ization		X	X	X (every 4 weeks)		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B+R, bendamustine and rituximab; BP, blood pressure; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EDC, electronic data capture; 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; IGHV, immunoglobulin heavy-chain variable region; MRD, minimal residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PK, pharmacokinetic PRO, patient-reported outcome; SAE, serious adverse event.

a. Patients will enter Long-term Follow-up after disease progression. Patients in Long-term Follow-up will be followed for their next CLL/SLL anticancer therapy, including date of progression following next line therapy, any new second primary malignancy (regardless of severity and relationship to study drug), and for survival. Contact will be in person or via phone (with the patient's guardian, if applicable) approximately every 12 weeks until death or study end, whichever comes first.
   NOTE: Patients in Arm B who receive approval for and initiate next-line "crossover" therapy with zanubrutinib will follow the Schedule of Assessments for Arms A and C instead of entering Long-term Follow-up after disease progression (see Section 5.13). Patients who initiate next-line ("crossover") treatment

with zanubrutinib will enter Long-term Follow-up at the time of subsequent disease progression per investigator assessment after starting zanubrutinib. Response assessments after crossover will occur per investigator assessment and will not be performed by independent central review.

b. Efficacy assessments are performed every 12 weeks after day of first dose for 96 weeks (approximately 24 months), then every 24 weeks. To avoid duplication of physical examinations, examination of liver and spleen, and laboratory tests to fulfill the separate Safety and Efficacy requirements, the following guideline may be used: It is not necessary to perform duplicate assessments so long as each Cycle Visit and Response Evaluation Visit window is met. At the time of an interim or primary analysis, sites may be asked to schedule visits for patients who are at least 2 months but not yet 3 months out from an unconfirmed best response. The visit would include a physical exam of the liver, spleen, and lymph nodes and hematology labs.
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. After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet together with source documentation/Supporting Documentation for Approval form with screening information and email it to the medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.
e. Patients will be placed into 1 of 4 cohorts based on the presence or absence of the 17p deletion as determined by the central laboratory testing: Cohort 1/1a (without del17p), Cohort 2 (with del17p), or Cohort 3 (with del17p or pathogenic TP53 variant [see Appendix 18]). Cohort 1a will be opened to enrollment in China when the Cohort 1 sample size has been reached. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached. Central randomization (1:1) will be used to assign patients in Cohort 1 to one of the following study drug treatments: Arm A: zanubrutinib or Arm B: bendamustine plus rituximab. Study treatment should be commenced within 5 days after randomization/treatment assignment.
f. Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Zanubrutinib dispensing and accountability 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 returned to the study personnel for review, 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 (eg, on or before the Safety Follow-up visit). The patient diary is not applicable during the Post-treatment Follow-up phase.
   For the purposes of the interim and final analyses, patients may be contacted in between visits to collect drug accountability data, which will be included in the EDC system.
g. Sparse zanubrutinib PK samples will be collected from all patients assigned to Arm A (Cohort 1/1a) and Arm C (zanubrutinib) at predose (< 30 min) and 2 hours (± 30 min) postdose on the first dose date and Cycle 2, Day 1 for the morning dose only. The time of zanubrutinib administration will be recorded. NOTE: PK samples are not required from patients who crossover from Arm B.
h. An echocardiogram, multigated acquisition scan (MUGA), or gated heart pool scan (GHPS) will be performed within 90 days of enrollment (ie, a standard of care procedure performed prior to consent for this study may be used if within window), and as medically necessary.
i. 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).
j. A 12-lead electrocardiogram (ECG) will be performed in triplicate (at least 1 minute apart) at screening. QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility.
k. Collect all AE information from the time of first dose of study drug until 30 days after the last dose of study drug or until disease progression, whichever occurs later. Collect SAE information from the time of signed informed consent through screen failure, until 30 days after the last dose of study treatment, or until disease progression, whichever occurs later. 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. See Section 8.4.1 for details.

l. Performed approximately 30 days after final dose of zanubrutinib including for patients who initiate a new anticancer therapy for CLL/SLL. May be combined with a required Post-treatment Follow-up clinic visit so long as both visits adhere to specified visit windows. Includes physical examination, vital signs, complete blood count, chemistry, ECOG PS, concomitant medication review, and AE review.

m. 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.

n. All patients must have baseline imaging within 35 days of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and 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 to be performed at screening, then approximately every 12 weeks after the first dose date for 96 weeks (approximately 24 months), then approximately every 24 weeks thereafter, until disease progression (including for patients who have discontinued or completed study treatment), withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. 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. Copies of all scans will be sent for independent central review for response assessment. At the time of suspected disease progression, imaging should be provided to the independent central review facility as soon as possible to enable prompt central assessment for disease progression. NOTE: For patients in Arm B who enter crossover, submission of scans for independent central review will be discontinued starting on the day of the first zanubrutinib dose. See Section 5.7 for additional details, including contraindication information.

o. Bone marrow biopsy is required within 90 days before enrollment. In lieu of performing a bone marrow procedure, a site can submit 10 slides from a previously performed diagnostic bone marrow biopsy if available. For patients with SLL, bone marrow aspirate may be provided for the central del17p FISH testing in addition to the peripheral blood sample.
Bone marrow biopsy and aspirate are required under the following conditions during the Treatment period and Post-treatment Follow-up phase starting at Week 36: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy and aspirate to confirm a CR or CRi (minimal residual disease assessment will also be assessed in the bone marrow and/or blood at this time); in cases of progression of cytopenias unrelated to autoimmune cytopenias or study treatment, perform a bone marrow biopsy and aspirate to confirm progressive disease. NOTE: The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia). This 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 at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression. Once CR in the bone marrow has been confirmed, no further bone marrow biopsy and aspirate are required unless otherwise clinically indicated. After Week 36, bone marrow biopsy and aspirate are required annually only for cases with suspected CR/CRi until CR in the bone marrow is confirmed. All the bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory. In addition, sites have the option to submit other specimens that may provide evidence of disease progression, such as tissue biopsy or blood sample, to the central pathology lab for analysis (eg, Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).

p. PROs will be collected prior to administration of study drug and medical procedures at baseline (first dose date), every 12 weeks after day of first dose for 96 weeks (approximately 24 months), and then every 24 weeks thereafter until disease progression. If feasible, patients must complete QOL questionnaires before performing any other procedures or study drug administration scheduled for that visit. NOTE: PROs are not required from patients who crossover from Arm B.

q. Complete blood count and differential will be evaluated by a central laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell 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. For instructions regarding the use of central versus local laboratories for hematology assessments, see Section 5.9.

r. Serum chemistry will be evaluated by a central 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.

s. The following 2 chemistry tests will only be done at screening and will be performed locally or at a central laboratory: 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.

t. Serum immunoglobulin evaluations (IgG, IgM, IgA) will be performed at Screening or baseline, then at Cycles 4, 7, 10, 13, and then every 24 weeks thereafter during the Treatment phase and Post-treatment Follow-up phases.

u. The coagulation profile will be performed at screening only. Prothrombin time (reported as international normalized ratio) and activated partial thromboplastin time will be evaluated by a central laboratory.

v. Prospective baseline test results for del17p are required for enrollment, and a single valid test result by central laboratory for del17p is needed. A blood sample will be collected at Screening for the evaluation of del17p by FISH. The protocol-required FISH test is not required to fall within the 35-day screening window before enrollment. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline del17p is needed. An exploratory assessment of cytogenetics may be performed. See Laboratory Manual for details.

w. Blood will be collected at Screening for the assessment of disease burden at baseline and will also be collected at the time of confirmed CR/CRi for the assessment of MRD.

x. Prospective baseline biomarker test results for IGHV are required for enrollment. A blood sample will be collected at Screening for assessment of IGHV mutational status by molecular methods. Local IGHV testing may be used for this study and may be performed outside of the 35-day screening window but not greater than 90 days. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline IGHV is needed.

y. A blood sample already being collected at Screening will be used for the assessment of molecular markers of disease. A separate blood sample will be collected at the time of confirmed clinical CR or CRi for the measurement of minimal residual disease by molecular methods. See the Laboratory Manual for details.

z. Patients receiving zanubrutinib who have progressive disease will be asked to provide a blood sample for the assessment of Mechanisms of Resistance (MOR) – relevant BTK pathway genes for specific mutations that have been identified as markers of resistance (such as, but not limited to BTK and PLCy). This sample is optional. See Laboratory Manual for details.

aa. The required screening for hepatitis B testing includes HBsAg, HBcAb, and HBsAb, as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status) – see Section 5.9. Patients who are HBcAb positive, HBsAg negative, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) as outlined in Section 5.9. All hepatitis B and hepatitis C testing will be performed by local laboratories unless central laboratory testing is required by the site.

bb. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening within 7 days of randomization and at end of treatment, and urine or serum pregnancy tests will be performed every 4 weeks (28 days) until end of treatment. Patients should then be tested at the 30-day safety follow up and at 60 and 90 days after the end of treatment. Pregnancy tests will be evaluated by either local or central laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

APPENDIX 11. SCHEDULE OF ASSESSMENTS FOR ARM B (BENDAMUSTINE + RITUXIMAB)

Study Period or Visit	**Screening**	**Treatment Phase (1 cycle ~ 28 days)**					**Post-Treatment Phase**		**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**			**Cycle 2 to 6**		**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks for 96 weeks (approximately 24 months) then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**0**	**1**	**2**	**1**	**2**	**1**	**Any day in the week**	
Window (Days)	–				**± 4**	**± 4**	**± 14**	**± 14**	**± 14**
Informed consent, screen number[c]	X								
Medical and cancer history	X								
Eligibility authorization packet[d]	X								
Cohort and arm assignment[e]	X								
Rituximab infusion[f]		X			X				
Bendamustine infusion[g]			X	X	X	X			
Safety Assessments[h]									
Echocardiogram[i]	X								
Vital signs (temperature, BP, heart rate)	X	X	X	X[cc]	X	X[cc]	X		
Physical examination[j]	X	X	X	X[cc]	X	X[cc]	X		
ECOG performance status	X	X	X	X[cc]	X	X[cc]	X		
12-Lead ECG (local read)[k]	X								
Concomitant medications review	X	X	X	X	X	X	X		
AE review[l]		X	X	X	X	X	X		X
Safety Follow-up Visit[m]		X							
Efficacy Assessments									
Disease-related constitutional symptoms	X							X	
Physical examination of liver, spleen and lymph nodes[n]	X							X	

Study Period or Visit	**Screening**	**Treatment Phase (1 cycle ~ 28 days)**					**Post-Treatment Phase**		**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**			**Cycle 2 to 6**		**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks for 96 weeks (approximately 24 months) then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**0**	**1**	**2**	**1**	**2**	**1**	**Any day in the week**	
Window (Days)	–				**± 4**	**± 4**	**± 14**	**± 14**	**± 14**
CT with IV and oral contrast[o]	X							X	
Bone marrow examination[p]	X							X	
PRO questionnaires[q]		X						X	
Overall response assessment								X	
Survival status and anticancer therapy									X
Laboratory Assessments									
Hematology[r], chemistry[s,t]	X	X	X		X	X	X	X	
Serum immunoglobulins[u]	X				X		X		
Coagulation[v]	X								
del17p (FISH), cytogenetics[w]	X								
Peripheral blood flow cytometry for MRD[x]	X							X	
Peripheral blood for IGHV mutation analysis[y]	X								
Peripheral blood for molecular markers of disease sample[z]	X							X	
Hepatitis B and C testing[aa]	X								
Pregnancy test (if applicable)[bb]	X within 7 days before random-ization				X		X (every 4 weeks)		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B+R, bendamustine and rituximab; BP, blood pressure; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; 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; IGHV, immunoglobulin heavy-chain variable region; MOR, mechanism of resistance; MRD, minimal residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PRO, patient-reported outcome; SAE, serious adverse event.

a. Patients will enter Long-term Follow-up after disease progression. Patients in Long-term Follow-up will be followed for their next CLL/SLL anticancer therapy, including date of progression following next line therapy, any new second primary malignancy (regardless of severity and relationship to study drug), and for survival. Contact will be in person or via phone (with the patient's guardian, if applicable) approximately every 12 weeks until death or study end, whichever comes first.
   NOTE: Patients in Arm B who receive approval for and initiate next-line "crossover" therapy with zanubrutinib will follow the Schedule of Assessments for Arms A and C instead of entering Long-term Follow-up after disease progression (see Section 5.13). Patients who initiate next-line ("crossover") treatment with zanubrutinib will enter Long-term Follow-up at the time of subsequent disease progression per investigator assessment after starting zanubrutinib. Response assessments after crossover will occur per investigator assessment and will not be performed by independent central review. Before crossover, patients in Arm B must complete the laboratory and safety tests required for crossover and imaging of the neck, chest, abdomen, and pelvis within 90 days of initiating crossover study drug treatment. Patients being considered for crossover who do not initiate crossover treatment within approximately 3 months after independent central review-confirmed disease progression should be contacted approximately every 12 weeks (either in person or by phone) to check survival status and for any new second primary malignancy, to confirm continued interest in crossover treatment, and to confirm if any non-protocol CLL/SLL anticancer therapies were initiated.
b. Efficacy assessments are performed every 12 weeks after day of first dose for 96 weeks (approximately 24 months), then every 24 weeks. To avoid duplication of physical examinations, examination of liver and spleen, and laboratory tests to fulfill the separate Safety and Efficacy requirements, the following guideline may be used: It is not necessary to perform duplicate assessments so long as each Cycle Visit and Response Evaluation Visit window is met. At the time of an interim or primary analysis, sites may be asked to schedule visits for patients who are at least 2 months but not yet 3 months out from an unconfirmed best response. The visit would include a physical exam of the liver, spleen, and lymph nodes and hematology labs.
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. After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet together with source documentation/Supporting Documentation for Approval form with screening information and email it to the medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.
e. Patients will be placed into 1 of 4 cohorts based on the presence or absence of the 17p deletion as determined by the central laboratory testing: Cohort 1/1a (without del17p), Cohort 2 (with del17p), or Cohort 3 (with del17p or pathogenic TP53 variant [see Appendix 18]). Cohort 1a will be opened to enrollment in China when the Cohort 1 sample size has been reached. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached. Central randomization (1:1) will be used to assign patients in Cohort 1 to one of the following study drug treatments: Arm A: zanubrutinib or Arm B: bendamustine plus rituximab. Study treatment should be commenced within 5 days after randomization/treatment assignment.
f. Rituximab will be administered intravenously at a dose of 375 mg/m^2 on the first day of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2 to 6.
g. Bendamustine will be administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles.
h. Patients receiving B+R will undergo safety assessments on Day 1 and 2 of Cycles 1 to 6 as well as on Day 0 of Cycle 1.

i. An echocardiogram, multigated acquisition scan (MUGA), or gated heart pool scan (GHPS) will be performed within 90 days of enrollment (ie, a standard of care procedure performed prior to consent for this study may be used if within window), and as medically necessary.
j. Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight once per cycle (height needed once at any predose timepoint).
k. A 12-lead electrocardiogram (ECG) will be performed in triplicate (at least 1 minute apart) at screening. QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility.
l. Collect all AE information from the time of first dose of study drug until 90 days after the last dose of study drug or until disease progression, whichever occurs later. Collect SAE information from the time of signed informed consent through screen failure, 90 days after the last dose of study drug, or until disease progression, whichever occurs later. 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. See Section 8.4.1 for details.
m. Performed approximately 30 days after the final dose of rituximab. Patients who received bendamustine will have a second safety follow-up visit approximately 90 days after the last dose of bendamustine. May be combined with a required Post-treatment Follow-up clinic visit so long as both visits adhere to specified visit windows. Includes physical examination, vital signs, complete blood count, chemistry, ECOG PS, concomitant medication review, and AE review.
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 of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and 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 to be performed at screening, then approximately every 12 weeks after the first dose date for 96 weeks (approximately 24 months), then approximately every 24 weeks thereafter, until disease progression (including for patients who have discontinued or completed study treatment), withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. 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. Copies of all scans will be sent to the independent central review for response assessment. At the time of suspected disease progression, imaging should be provided to the independent central review facility as soon as possible to enable prompt central assessment for disease progression. NOTE: For patients in Arm B who enter crossover, submission of scans for independent central review will be discontinued starting on the day of the first zanubrutinib dose. See Section 5.7 for additional details, including contraindication information.
p. Bone marrow biopsy is required within 90 days before enrollment. In lieu of performing a bone marrow procedures, a site can submit 10 slides from a previously performed diagnostic bone marrow biopsy if available. For patients with SLL, bone marrow aspirate may be provided for the central del17p FISH testing in addition to the peripheral blood sample.
Bone marrow biopsy and aspirate are required under the following conditions during the Treatment period and Post-treatment Follow-up phase starting at Week 36: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy and aspirate to confirm a CR or CRi (minimal residual disease assessment will also be assessed in the bone marrow and/or blood at this time); in cases of progression of cytopenias unrelated to autoimmune cytopenias or study treatment, perform a bone marrow biopsy and aspirate to confirm progressive disease. NOTE: The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia). This 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 at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression. Once CR in the bone marrow has been confirmed, no further bone marrow biopsy and aspirate are required unless otherwise clinically indicated. After Week 36, bone marrow biopsy and aspirate are required annually only for cases with suspected CR/CRi until CR in the bone marrow is confirmed. All the bone marrow samples will be collected and reviewed by a pathologist from the central

pathology laboratory. In addition, sites have the option to submit other specimens that may provide evidence of disease progression, such as tissue biopsy or blood sample, to the central pathology lab for analysis (eg, Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).

q. PROs will be collected prior to administration of study drug and medical procedures at baseline (first dose date), every 12 weeks after day of first dose for 96 weeks (approximately 24 months), and then every 24 weeks thereafter until disease progression. If feasible, patients must complete QOL questionnaires before performing any other procedures or study drug administration scheduled for that visit.

r. Complete blood count and differential will be evaluated by a central laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell 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. For instructions regarding the use of central versus local laboratories for hematology assessments, see Section 5.9.

s. Serum chemistry will be collected by a central 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 or at a central laboratory: 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. Serum immunoglobulin evaluations (IgG, IgM, IgA) will be performed at Screening or baseline, then at Cycles 4, 7, 10, 13, and then every 24 weeks thereafter during the Treatment phase and Post-treatment Follow-up phases.

v. The coagulation profile will be performed at screening only. Prothrombin time (reported as international normalized ratio) and activated partial thromboplastin time will be evaluated by a central laboratory.

w. Prospective baseline test results for del17p are required for enrollment and a single valid test result by central laboratory for del17p is needed. A blood sample will be collected at Screening for the evaluation of del17p by FISH. The protocol-required FISH test is not required to fall within the 35-day screening window before enrollment. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline del17p is needed. An exploratory assessment of cytogenetics may be performed. See Laboratory Manual for details.

x. Blood will be collected at Screening for the assessment of disease burden at baseline and will also be collected at the time of confirmed CR/CRi for the assessment of MRD.

y. Prospective baseline biomarker test results for IGHV are required for enrollment. A blood sample will be collected at Screening for assessment of IGHV mutational status by molecular methods. Local IGHV testing may be used for this study and may be performed outside of the 35-day screening window but not greater than 90 days. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline IGHV is needed.

z. A blood sample will be collected at Screening for the assessment of molecular markers of disease and at the time of confirmed clinical CR or CRi for the measurement of minimal residual disease by molecular methods.

aa. The required screening for hepatitis B testing includes HBsAg, HBcAb, and HBsAb, as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status) – see Section 5.9. Patients who are HBcAb positive, HBsAg negative, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) as outlined in Section 5.9. All hepatitis B and hepatitis C testing will be performed by local laboratories unless central laboratory testing is required by the site.

bb. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening within 7 days of randomization and at end of treatment, and urine or serum pregnancy tests will be performed every 4 weeks (28 days) until end of treatment. Patients

before crossover should be tested at the 30-day safety follow up, at 60 days after the end of treatment, and at the 90-day safety follow up. Patients after crossover should be tested at the 30-day safety follow up and at 60 and 90 days after the end of treatment. Pregnancy tests will be evaluated by local or central laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

cc. On Day 2 of each treatment cycle, vital signs, physical examination, and ECOG performance status are required only if clinically indicated.

APPENDIX 12. SCHEDULE OF ASSESSMENTS FOR ARM D (VENETOCLAX + ZANUBRUTINIB)

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycles 2 and 3**	**Cycle 4 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 108 weeks (approximately 27 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 7[c]**	**± 14**	**± 14[d]**	**± 14**
Informed consent, screen number[e]	X						
Medical and cancer history	X						
Eligibility authorization packet[f]	X						
Cohort and arm assignment[g]	X						
Zanubrutinib dispensing and accountability[h]		X	X	X	**X[i]**		
Sparse zanubrutinib PK sampling[j]		X	X				
Zanubrutinib and venetoclax PK sampling[jj]				X[jj]	X[jj]		
Venetoclax dispensing and accountability[k]				X[kk]	**X[l]**		
Safety Assessments							
Echocardiogram[m]	X						
Vital signs (temperature, BP, heart rate)[n]	X	X	X	X	X		
Physical examination[o]	X	X	X	X	X		

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycles 2 and 3**	**Cycle 4 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 108 weeks (approximately 27 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 7[c]**	**± 14**	**± 14[d]**	**± 14**
ECOG performance status	X	X	X	X	X		
12-Lead ECG (local read)[p]	X						
TLS risk category[ll]	X		X				
Concomitant medications review	X	X	X	X	X		
AE review[q]		X	X	X	X		X
Safety Follow-up Visit[r]		X					
Efficacy Assessments							
Disease-related constitutional symptoms	X					X	
Physical examination of liver, spleen and lymph nodes[s]	X					X	
CT with IV and oral contrast[t]	X					X	
Bone marrow examination[u]	X					X	
PRO questionnaires[v]		X				X	
Overall response assessment						X	
Survival status and new anticancer therapy							X

Study Period or Visit	**Screening**	**Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)**					**Long-Term Follow-Up[a]**
Cycle/Week	–	**Cycle 1**	**Cycles 2 and 3**	**Cycle 4 to 6**	**Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression**	**Response Evaluation Every 12 weeks from start of Cycle 1 for 108 weeks (approximately 27 months), then every 24 weeks until disease progression[b]**	**Approximately every 12 weeks**
Day	**-35 to date of enrollment**	**1**	**1**	**1**	**1**	**Any day in the week**	
Window (Days)	–		**± 4**	**± 7[c]**	**± 14**	**± 14[d]**	**± 14**
Laboratory Assessments							
Hematology[w], chemistry[x,y]	X	X	X	X	X	X	
Serum immunoglobulins[z]	X			X	X		
Coagulation[aa]	X						
del17p (FISH)[bb], cytogenetics[bb]	X						
TP53 mutational analysis[mm]	X						
Peripheral blood flow cytometry/undetectable MRD4[cc]	X					X	
Bone marrow aspirate flow cytometry/ undetectable MRD4[dd]						X	
Peripheral blood for IGHV mutation analysis[ee]	X						
Peripheral blood for molecular markers of disease sample[ff]	X					X	
Peripheral blood for mechanisms of resistance biomarker sample[gg]						X	

Study Period or Visit	Screening	Treatment and Post-Treatment Follow-Up (1 cycle ~ 28 days)					Long-Term Follow-Up[a]
Cycle/Week	–	Cycle 1	Cycles 2 and 3	Cycle 4 to 6	Cycle 7 then every 3 cycles (eg, Cycle 7, 10, 13, etc) until disease progression	Response Evaluation Every 12 weeks from start of Cycle 1 for 108 weeks (approximately 27 months), then every 24 weeks until disease progression[b]	Approximately every 12 weeks
Day	-35 to date of enrollment	1	1	1	1	Any day in the week	
Window (Days)	–		± 4	± 7[c]	± 14	± 14[d]	± 14
Hepatitis B and C testing[hh]	X						
Pregnancy test (if applicable)[ii]	X within 7 days before random-ization		X	X	X (every 4 weeks)		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B+R, bendamustine and rituximab; BP, blood pressure; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; 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; IGHV, immunoglobulin heavy-chain variable region; MRD, minimal residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PK, pharmacokinetic PRO, patient-reported outcome; SAE, serious adverse event; undetectable MRD4, undetectable minimal residual disease at $< 10^{-4}$ sensitivity; TLS, tumor lysis syndrome.

a. Patients will enter Long-term Follow-up after disease progression. Patients in Long-term Follow-up will be followed for their next CLL/SLL anticancer therapy, including date of progression following next line therapy, any new second primary malignancy (regardless of severity and relationship to study drug), and for survival. Contact will be in person or via phone (with the patient's guardian, if applicable) approximately every 12 weeks until death or study end, whichever comes first.
b. Efficacy assessments are performed every 12 weeks after day of first dose for 108 weeks (approximately 27 months), then every 24 weeks. To avoid duplication of physical examinations, examination of liver and spleen, and laboratory tests to fulfill the separate Safety and Efficacy requirements, the following guideline may be used: It is not necessary to perform duplicate assessments so long as each Cycle Visit and Response Evaluation Visit window is met. At the time of an interim or primary analysis, sites may be asked to schedule visits for patients who are at least 2 months but not yet 3 months out from an unconfirmed best response. The visit would include a physical exam of the liver, spleen, and lymph nodes and hematology labs.
c. To allow for enough time to assess tumor lysis syndrome risk categorization in Arm D, the allowed window for Cycle 4 will be ± 14 days. The assessment of tumor lysis syndrome risk categorization at the end of Cycle 3 must be completed before dosing with venetoclax is initiated (see Section 6.2.3.1).
d. The window for BM aspirates will be ± 28 days.
e. 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.
f. After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet together with source documentation/Supporting Documentation for Approval form with screening information and email it to the

medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.

g. Patients will be placed into 1 of 4 cohorts based on the presence or absence of the 17p deletion as determined by the central laboratory testing: Cohort 1/1a (without del17p), Cohort 2 (with del17p), or Cohort 3 (with del17p or pathogenic TP53 variant [see Appendix 18]). Cohort 1a will be opened to enrollment in China when the Cohort 1 sample size has been reached. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached. Central randomization (1:1) will be used to assign patients in Cohort 1 to one of the following study drug treatments: Arm A: zanubrutinib or Arm B: bendamustine plus rituximab. Study treatment should be commenced within 5 days after randomization/treatment assignment.
h. Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Zanubrutinib dispensing and accountability will be provided to each patient to record the study drug dose taken each day. Dispensation and accountability for zanubrutinib will occur each cycle and may require patients to return to the site/pharmacy every cycle while venetoclax is being administered. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the study personnel for review, 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 (eg, on or before the Safety Follow-up Visit). The patient diary is not applicable during the Post-Treatment Follow-up phase.
i. Unless otherwise agreed by the medical monitor, zanubrutinib will be permanently discontinued after Cycle 27 if the patient has confirmed CR/CRi, meets undetectable minimal residual disease at $< 10^{-4}$ sensitivity (undetectable MRD4) criteria in 2 consecutive peripheral blood samples, and meets undetectable MRD4 criteria in 2 consecutive bone marrow aspirate samples at least 12 weeks apart (see Section 6.2.1).
j. Sparse zanubrutinib PK samples will be collected from all patients assigned to Arm D (zanubrutinib monotherapy run-in) at predose (< 30 min) and 2 hours (± 30 min) postdose on the first dose date and on Cycle 2, Day 1 for the morning dose only. The time of zanubrutinib administration will be recorded.
k. Dispensation and accountability for venetoclax will occur each cycle and may require patients to return to the site/pharmacy every cycle. 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 4, Days 1 through 7, 50 mg on Cycle 4, Days 8 through 14, 100 mg on Cycle 4, Days 15 through 21, 200 mg on Cycle 4, Days 22 through 28, and 400 mg from Cycle 5, Day 1 through Cycle 27.
l. Venetoclax will be permanently discontinued after Cycle 15 if the patient has confirmed CR/CRi, meets undetectable MRD4 criteria in 2 consecutive peripheral blood samples, and meets undetectable MRD4 criteria in 2 consecutive bone marrow aspirates at least 12 weeks apart (see Section 6.2.3).
m. An echocardiogram, multigated acquisition scan (MUGA), or gated heart pool scan (GHPS) will be performed within 90 days of enrollment (ie, a standard of care procedure performed prior to consent for this study may be used if within window), and as medically necessary.
n. In addition to the vital signs required for each cycle visit, vital signs will be performed along with serum chemistry and hematology timepoints for TLS monitoring as clinically indicated for the initial venetoclax dose and each dose increase. See Section 6.2.3.1, Appendix 14, and Appendix 15 for further details.
o. 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).
p. A 12-lead electrocardiogram (ECG) will be performed in triplicate (at least 1 minute apart) at screening. QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility.
q. Collect all AE information from the time of first dose of study drug until 30 days after the last dose of study drug or until disease progression, whichever occurs later. 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 occurs later. 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. See Section 8.4.1 for details.

r. Performed approximately 30 days after final dose of zanubrutinib, including for patients who initiate a new anticancer therapy for CLL/SLL. May be combined with a required Post-Treatment Follow-up clinic visit so long as both visits adhere to specified visit windows. Includes physical examination, vital signs, complete blood count, chemistry, ECOG PS, concomitant medication review, and AE review.
s. 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.
t. All patients must have baseline imaging within 35 days of randomization. CT scan with IV and oral contrast of the neck, chest, abdomen, and 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 to be performed at screening, then approximately every 12 weeks after the first dose date for 108 weeks (approximately 27 months), then approximately every 24 weeks thereafter, until disease progression (including for patients who have discontinued or completed study treatment), withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. 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. Copies of all scans will be sent for potential independent central review for response assessment. See Section 5.7 for additional details, including contraindication information.
u. Bone marrow biopsy is required within 90 days before enrollment. In lieu of performing a bone marrow procedure, a site can submit 10 slides from a previously performed diagnostic bone marrow biopsy if available. For patients with SLL, bone marrow aspirate may be provided for the central del17p FISH testing in addition to the peripheral blood sample.
Bone marrow core biopsy and aspirate are required under the following conditions during the Treatment period and Post-treatment Follow-up phase starting at Week 36: if clinical and laboratory results demonstrate a potential CR or CRi, perform a bone marrow biopsy and aspirate to confirm a CR or CRi (minimal residual disease assessment will also be assessed in the bone marrow and/or blood at this time); in cases of progression of cytopenias unrelated to autoimmune cytopenias or study treatment, perform a bone marrow biopsy and aspirate to confirm progressive disease. NOTE: The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia). This 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 at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.
After Week 36, bone marrow core biopsy and aspirate are required annually only for cases with suspected CR/CRi until CR/CRi in the bone marrow is confirmed. Patients with suspected CR or CRi whose bone marrow core biopsy shows morphologic evidence of disease may optionally undergo another bone marrow core biopsy and aspirate approximately 24 weeks from the most recent previous bone marrow examination. It is recommended to do this assessment if the patient has 2 consecutive tests showing negative peripheral blood MRD (see Section 5.10). All the bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory. In addition, sites have the option to submit other specimens that may provide evidence of disease progression, such as tissue biopsy or blood sample, to the central pathology lab for analysis (eg, Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).
v. PROs will be collected prior to administration of study drug and medical procedures at baseline (first dose date), every 12 weeks after day of first dose for 96 weeks (approximately 24 months), and then every 24 weeks thereafter until disease progression. If feasible, patients must complete QOL questionnaires before performing any other procedures or study drug administration scheduled for that visit.
w. Complete blood count and differential will be evaluated by a central laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell 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. For instructions regarding the use of central versus local laboratories for hematology assessments, see Section 5.9.
For venetoclax dosing: For patients with low, medium or high TLS risk, refer to Appendix 14 for hematology timepoints. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. 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 initiated. Additional laboratory assessments may be performed per investigator discretion. See Section 6.2.3.1, Appendix 15, and the Laboratory Manual for further details.

x. Serum chemistry will be evaluated by a central 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.
   For venetoclax dosing: For patients with low, medium, or high TLS risk, refer to Appendix 14 for serum chemistry (including uric acid) timepoints. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. 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 initiated. Additional laboratory assessments may be performed per investigator discretion. See Section 6.2.3.1, Appendix 15, and the Laboratory Manual for further details.
y. The following 2 chemistry tests will only be done at screening and will be performed locally or at a central laboratory: 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.
z. Serum immunoglobulin evaluations (IgG, IgM, IgA) will be performed at Screening or baseline, then at Cycles 4, 7, 10, 13, and then every 24 weeks thereafter during the Treatment phase and Post-treatment Follow-up phases.
aa. The coagulation profile will be performed at screening only. Prothrombin time (reported as international normalized ratio) and activated partial thromboplastin time will be evaluated by a central laboratory.
bb. Prospective baseline test results for del17p are required for enrollment and a single valid test result by central laboratory for del17p is needed. A blood sample will be collected at Screening for the evaluation of del17p by FISH. The protocol-required FISH test is not required to fall within the 35-day screening window before enrollment. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline del17p is needed. An exploratory assessment of cytogenetics may be performed. See the Laboratory Manual for details.
cc. Peripheral blood will be collected for undetectable MRD4 analysis by flow cytometry and molecular methods at Screening.
   Starting at Week 12, peripheral blood samples will be collected at every scheduled response assessment for undetectable MRD4 analysis. Patients with confirmed CR or CRi and two consecutive tests showing undetectable MRD in peripheral blood approximately 12 weeks from each other will undergo bone marrow aspiration for MRD assessment (see footnote dd).
   So long as the peripheral blood MRD is undetectable, patients will undergo repeat bone marrow aspirate every approximately 48 weeks until two consecutive tests show undetectable MRD in the bone marrow. It is recommended, but not required, to undergo repeat bone marrow aspirate approximately every 12 weeks after the first bone marrow MRD assessment, until two consecutive tests show undetectable MRD, as long as peripheral blood MRD also remains negative. See the Laboratory Manual for details.
dd. After Week 112, if bone marrow aspirate continues to show detectable MRD, patients who remain in CR or CRi and have continued peripheral blood MRD negativity may optionally undergo bone marrow aspirates for assessment of MRD. These bone marrow aspirates may be collected every approximately 24 weeks, until two consecutive tests (≥ 12 weeks apart) show undetectable MRD.
   Patients requiring additional bone marrow assessments for MRD only require aspirate – no core biopsy is required except when clinically indicated (see Section 5.7). See the Laboratory Manual for details.
ee. Prospective baseline biomarker test results for IGHV are required for enrollment. A blood sample will be collected at Screening for assessment of IGHV mutational status by molecular methods. Local IGHV testing may be used for this study and may be performed outside of the 35-day screening window but

not greater than 90 days. If a patient is not enrolled as part of the initial study screening, and later decides to be re-screened, contact the medical monitor to ask whether re-testing of baseline IGHV is needed.

ff. A blood sample already being collected at Screening will be used for the assessment of molecular markers of disease. A separate blood sample will be collected at the time of confirmed clinical CR or CRi for the measurement of minimal residual disease by molecular methods. See the Laboratory Manual for details.

gg. Patients receiving zanubrutinib who have progressive disease will be asked to provide a blood sample for the assessment of Mechanisms of Resistance (MOR) - relevant BTK pathway genes for specific mutations that have been identified as markers of resistance (such as, but not limited to BTK and PLCy). This sample is optional. See the Laboratory Manual for details.

hh. The required screening for hepatitis B testing includes HBsAg, HBcAb, and HBsAb, as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status) – see Section 5.9. Patients who are HBcAb positive, HBsAg negative, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) as outlined in Section 5.9. All hepatitis B and hepatitis C testing will be performed by local laboratories unless central laboratory testing is required by the site.

ii. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening within 7 days of randomization and at end of treatment, and urine or serum pregnancy tests will be performed every 4 weeks (28 days) until end of treatment. Patients should then be tested at the 30-day safety follow up and at 60 and 90 days after the end of treatment. Pregnancy tests will be evaluated by either local or central laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

jj. This optional PK sub-study, designed to assess potential drug-drug interactions between zanubrutinib and venetoclax, will include patients who have received zanubrutinib 160 mg twice a day for at least 5 consecutive days and 400 mg venetoclax daily for at least 1 week prior to the day of sample collection. Blood samples for PK analysis of zanubrutinib and venetoclax will be collected on Day 1 of Cycle 6 or any cycle beyond Cycle 6 (eg, Cycle 7, Cycle 10, etc) at the following timepoints: predose (≤ 30 min prior to morning dose) and postdose (2 hours [± 30 min], 4 hours [± 30 min], and 8 hours [± 2 hours] following the morning zanubrutinib dose. See Appendix 17.

kk. Serum chemistry and hematology laboratory samples (performed locally) must be drawn any time within 4 hours prior to the first dose of venetoclax and subsequent dose increases. Electrolyte values (including uric acid, potassium, phosphate and calcium) should be reviewed and should not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax. 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 initiated (see Section 6.2.3.1 and Appendix 16).

ll. All patients assigned to Arm D must have an assessment of TLS risk category completed at screening and at the end of Cycle 3 (must be completed before dosing with venetoclax is initiated). Imaging and hematology laboratory results are required for TLS risk assessment; please refer to Section 6.2.3.1 for details.

mm. TP53 mutational analysis is optional and may be performed in addition to the required central laboratory FISH testing for del17p. If the local TP53 test used a sample other than peripheral blood, a specimen from that same tissue sample, if available, should be sent to the central laboratory for potential future central TP53 testing. Requirements for local testing of TP53 status are provided in Appendix 18.

APPENDIX 13. CLL STAGING SYSTEM

Rai System[a]

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood > 5 x 10^9/L clonal B-cells and > 40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0-II with hemoglobin < 11 g/dL or hematocrit < 33%	High
IV[c]	Stage 0-III with platelets < 100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and < 3 enlarged areas*
B	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and ≥ 3 enlarged areas*
C[c]	Hemoglobin < 10 g/dL and/or Platelets < 100,000/mm^3 and any number of enlarged areas*

Source: NCCN Clinical Practice Guidelines in Oncology Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 3.2018.

a. This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, Chanana Ad, Levy RN, Pasternack BS. Clinical Staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. © The American Society of Hematology.

b. From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:196-206.

c. Immune-mediated cytopenias are not the basis for these stage definitions.
*Areas include liver, spleen, axillary region, inguinal region, and cervical region

APPENDIX 14. REQUIRED TUMOR LYSIS SYNDROME MONITORING FOR VENETOCLAX INITIATION

Hematology and Chemistry Monitoring for Venetoclax Ramp-Up Dosing Based on TLS Risk

TLS Risk	Required Hematology and Chemistry Monitoring				
	20 mg	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Low	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h
	Outpatient				
Medium[a,b]	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h
	Outpatient				
High[b,c]	Predose: within 4 h of venetoclax dose Postdose: at 4 and 8 h (± 30 min) and at 12 and 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: at 4 and 8 h (± 30 min) and at 12 and 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)	Predose: within 4 h of venetoclax dose Postdose: between 6-8 h and at 24 h (± 2 h)
	Requires Hospitalization		**Outpatient**		

Abbreviations: h, hour; TLS, Tumor Lysis Syndrome.

a. For first dose of 20 mg and 50 mg, consider hospitalization for patients at medium TLS risk with CrCl < 80 mL/min

b. Patients hospitalized for any ramp-up dosing must receive the following monitoring: pre-dose (within 4 h of venetoclax dose) and postdose (at 4 and 8 h [±30 min] and at 12 and 24 h [± 2 h] after dosing)

c. High-risk patients with CrCl ≥ 80 mL/min will receive the subsequent dose increases (after 50 mg) as outpatients. Patients with CrCl < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized.

APPENDIX 15. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME

FIRST DOSE OF VENETOCLAX OR DOSE INCREASE

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols. In addition to the recommendations in the table below, for patients with CLL/SLL receiving first dose of venetoclax:
- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow guideline.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal

Abnormality	Management Recommendations
	(ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. • If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV x 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV x 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. – If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.

Abnormality	Management Recommendations
	• Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Administer rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) OR Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus > 10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

IV, intravenous; ULN, upper limit of normal; WNL, within normal limits.

ONGOING DOSING OF VENETOCLAX

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (eg, 48 or 72 hours) are as below. NOTE: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

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

If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.

- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

In the event of laboratory TLS, if blood chemistry and symptoms resolve within 24 to 48 hours after the last dose, venetoclax can be resumed at the same dose. If blood chemistry and symptoms require > 48 hours to resolve or in the event of clinical TLS, venetoclax should be resumed at a reduced dose (refer to Table 7).

APPENDIX 16. DEFINITION AND GRADING OF TUMOR LYSIS SYNDROME

Definition of Laboratory and Clinical Tumor Lysis Syndrome

	Criterion	Metabolic/Clinical Abnormalities
Laboratory-TLS	The presence of two or more metabolic abnormalities in a patient with cancer, or undergoing treatment for cancer within three days prior to, and up to seven days after, initiation of treatment	• Uric acid ≥ 476 µmol/L or 25% increase from baseline • Potassium ≥ 6.0 mmol/L or 25% increase from baseline • Phosphate ≥ 1.45 mmol/L or 25% increase from baseline • Calcium ≤ 1.75 mmol/L or 25% decrease from baseline
Clinical-TLS	A patient with laboratory-TLS and at least one clinical abnormality	• Creatinine ≥ 1.5 x ULN (age > 12 years or age-adjusted) • Cardiac arrhythmia • Sudden death • Seizure

TLS, tumor lysis syndrome; ULN, upper limit of normal
Source: Jones et al 2015

Cairo-Bishop Grading System for Tumor Lysis Syndrome

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0[a]	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[b]	Death[b]	Death[b]

Abbreviations: ADL, activities of daily living; LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal
a. Grade 0 should not be used in this study unless all other possible explanations for acute kidney injury have been ruled out.
b. Probably or definitely contributable to clinical TLS
Source: Cairo et al 2004

APPENDIX 17. PHARMACOKINETIC SUB-STUDY FOR PATIENTS IN COHORT 3 (ARM D)

Introduction

This optional pharmacokinetic (PK) sub-study is designed to assess potential drug-drug interactions (DDI) between zanubrutinib and venetoclax. Patients enrolled in Cohort 3 of BGB-3111-304 (Arm D) who have received zanubrutinib 160 mg twice a day for at least 5 consecutive days and 400 mg venetoclax daily for at least 1 week prior to the day of sample collection will be evaluated.

Zanubrutinib and venetoclax are both primarily metabolized by Cytochrome P450 3A (CYP3A) enzymes. Following multiple oral administrations, the maximum plasma concentration (C_{max}) of venetoclax is typically reached 5 to 8 hours after dosing (VENCLEXTA USPI, Nov 2018; Venclyxto SmPC, May 2018). The terminal elimination half-life ($t_{1/2}$) of venetoclax is approximately 26 hours and the PK of venetoclax does not change over time.

Review of available in vitro and clinical data suggest a low DDI potential between venetoclax and zanubrutinib. Zanubrutinib did not inhibit CYP3A4 activity and showed only a weak inhibitory effect on the P-gp transporter (BGB-3111-108 Clinical Study Report; data on file).

Recent data have indicated that the mean AUC (58.6 µg•h/mL; n = 151) (Tam et al, 2019b) of venetoclax was higher when co-administered with ibrutinib than single-agent venetoclax (32.8 ± 16.9 µg•h/mL) (VENCLEXTA USPI, Nov 2018; Venclyxto SmPC, May 2018) but was within the AUC range observed in doses previously studied. Of note, venetoclax has high PK variability and a significant food effect. It has been shown that administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. To reduce the PK variability of venetoclax introduced by meal consumption for the DDI assessment, subjects in this sub-study are advised to consume a low-fat breakfast as detailed in the next section.

Study Procedures

Blood samples for PK analysis of venetoclax and zanubrutinib will be collected from consenting patients enrolled in Cohort 3 of BGB-3111-304 (Arm D; venetoclax + zanubrutinib) who have received zanubrutinib 160 mg twice a day for at least 5 consecutive days and 400 mg venetoclax daily for at least 1 week prior to the day of sample collection at the following timepoints:

Cycle 6 Day 1*: predose (≤ 30 min prior to morning dose) and postdose (2 hours [± 30 min], 4 hours [± 30 min], and 8 hours [± 2 hours]) following the morning zanubrutinib dose

**** NOTE: If the sample cannot be collected on Day 1 of Cycle 6, it may be collected on Day 1 of any cycle beyond Cycle 6 (eg, Cycle 7, Cycle 10, etc), as long as the patient's current study drug regimen includes zanubrutinib 160 mg twice a day for at least 5 consecutive days and venetoclax 400 mg daily for at least 1 week.***

On the day of PK sample collection, it is recommended that patients eat a low-fat breakfast in order to control for the food effect on the PK of venetoclax. There are no restrictions on food intake prior to dosing, such as an overnight fast. It is suggested to complete the breakfast within

30 minutes to 1 hour prior to dosing of zanubrutinib and venetoclax. Two examples of a low-fat breakfast are described below (US FDA Guidance for Industry 2019):

Example 1:

- Eight ounces milk (1 percent fat)
- One boiled egg
- One packet of flavored instant oatmeal made with water

Example 2:

- 1 egg fried in butter
- 2 slices of wheat toast with jelly
- 8 oz of 1% milk

It is recommended that patients wait until after the 4-hour postdose sample is collected to eat another meal.

On the day of PK sample collection, study drug administration must occur under the supervision of the investigator (or designee) after the predose PK sample is obtained. Zanubrutinib and venetoclax should be administered simultaneously with at least 240 mL (8 fluid ounces) of water, one after the other. The date and time of study drug administration and PK sample collection (including those prior to the day of PK sample collection) will be recorded in the eCRF. The actual date and time each sample was collected will be recorded to the nearest minute in the electronic case report form (eCRF). PK samples will only be collected from sites that are able to adequately follow the sampling, handling, and processing procedures outlined in this section.

Peripheral blood samples for PK analysis of zanubrutinib and venetoclax will be collected into potassium EDTA (K2-EDTA) collection tubes at the timepoints specified above. Approximately 4 mL of blood (2 mL for each study drug analysis) at each timepoint will be collected. Samples will be analyzed by the designated bioanalytical laboratory for quantification of plasma venetoclax and zanubrutinib concentrations using a validated method. Details concerning handling of the PK plasma samples, including labeling and shipping instructions, will be provided in the Laboratory Manual.

Pharmacokinetic Analysis

Plasma venetoclax and zanubrutinib concentrations will be summarized by scheduled time of collection.

If supported by the data, venetoclax PK from this sub-study will be compared to venetoclax PK reported in the literature.

A population PK analysis may be performed to include zanubrutinib plasma concentrations from this sub-study in an existing model.

Pharmacokinetic Blood Sampling: Arm D Venetoclax + Zanubrutinib

Procedure	**C6D1[a]**			
Hours	**Predose**	**2**	**4**	**8**
Window	≤ 30 min	± 30 min	± 30 min	± 2 h
PK blood sampling	X	X	X	X

Abbreviations: C, cycle; D, day; h, hour; min, minute; PK, pharmacokinetics

a. If patients miss the Cycle 6, Day 1 collection time, the sample may be collected on Day 1 of any cycle beyond Cycle 6 (eg, Cycle 7,10, etc.), as long as the patient's current study drug regimen includes zanubrutinib 160 mg twice a day for at least 5 consecutive days and venetoclax 400 mg once daily for at least 1 week.

NOTE: It is important that the PK sampling times should be consistent with their scheduled time. To achieve this, other assessment items at the same time are allowed to be advanced or delayed so that there is sufficient time to complete the blood sampling.

APPENDIX 18. REQUIREMENTS FOR LOCAL TESTING OF PATHOGENIC TP53 VARIANTS

For Arm D only, patients with a central fluorescence in situ hybridization (FISH) test result other than del17p-positive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) may meet eligibility for Inclusion Criterion 1 with a local laboratory test result documenting pathogenic TP53 variant(s) meeting the requirements shown below. Local TP53 mutational analysis is optional and may have been performed as part of the standard disease work-up. This appendix provides the requirements that must be met for local laboratory TP53 mutational test results to be accepted for the purposes of eligibility assessment for this study.

In general, the parameters listed below, which are based on the 2018 European Research Initiative on Chronic Lymphocytic Leukemia (ERIC) recommendations (Malcikova et al 2018), must be met to fulfill eligibility requirements. A redacted copy of a local TP53 mutational analysis report documenting these parameters should be provided and approved by the medical monitor as part of the eligibility approval process and prior to patient enrollment.

Material	No specific requirement. Examples include the following: peripheral blood collected in EDTA or heparin; bone marrow; or biopsies of lymph nodes or extranodal lesions (NOTE: fresh/frozen biopsy samples are preferred)
Coverage	Should cover exons 4 to 10; exons 2 to 11 preferred
Assay type	Bidirectional Sanger sequencing or next-generation sequencing
Minimum variant allele frequency	≥ 10% for all assays with a minimum sensitivity of ≤ 10% per local laboratory standard, OR Minimum laboratory standard may be used if sensitivity is > 10%
Acceptable pathogenic variants	Must be confirmed as pathogenic in either the IARC TP53 database (http://p53.iarc.fr/TP53GeneVariations.aspx) or the TP53 website (UMD database; http://p53.fr/). **Common polymorphisms and neutral variants will not be accepted**. Variants of unknown significance or variants that are not listed in either database may be acceptable with agreement by the medical monitor.

Abbreviations: IARC, International Agency for Research on Cancer.

For patients meeting Inclusion Criterion 1 due to having a pathogenic TP53 variant, the variant allele must be documented in the electronic case report form (eCRF) using standard Human Genome Variation Society (HGVS) nomenclature. The variant allele frequency, if available, should be documented as a percentage.

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Approval	[redacted] Clinical Development 10-Feb-2021 20:46:23 GMT+0000

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