This supplement contains the following items:

CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Identifier:	BGB-3111-305
Phase:	3
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. [redacted]
Reference Number:	EudraCT 2018-001366-42
Original Protocol:	09 July 2018

[redacted]

FINAL PROTOCOL APPROVAL SHEET

A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BeiGene, Ltd. Approval:

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Product: zanubrutinib (BGB-3111)
Title of Study: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Identifier: BGB-3111-305
Phase of Development: 3
Number of Patients: Approximately 400
Study Centers: Approximately 150

Study Objectives:
Primary
• To compare the efficacy of zanubrutinib (also known as BGB-3111) versus ibrutinib as measured by overall response rate determined by independent central review
Secondary
• To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
  o Progression-free survival determined by independent central review
  o Progression-free survival determined by investigator assessment
  o Duration of response determined by independent central review
  o Duration of response determined by investigator assessment
  o Time to treatment failure
  o Rate of partial response with lymphocytosis or higher determined by independent central review
  o Overall survival
  o Patient-reported outcomes
• To compare the safety of zanubrutinib versus ibrutinib

Exploratory

- [redacted]
- [redacted]

Study Design:

This is a Phase 3, randomized study of zanubrutinib versus ibrutinib in approximately 400 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Refractory disease is defined as either no objective response to or disease progression within 6 months of the last treatment, and relapsed disease is defined as patients whose disease relapses more than 6 months after the last treatment and subsequently progressed. The primary efficacy endpoint is overall response rate (ORR; partial response [PR] or higher) determined by independent central review. Disease response will be assessed per the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2008), with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2), and per Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) for patients with SLL (Appendix 3). Rate of response for PR-L or higher will be assessed as a secondary efficacy endpoint.

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del[17p]/TP53 mutation status (present or absent). [redacted]

Treatment with zanubrutinib and ibrutinib will be open label. Study treatment must commence within 5 days after randomization/treatment assignment and will be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination. Each cycle consists of 28 days. Based on enrollment prediction and the estimated treatment duration, [redacted]

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; laboratory studies; bone marrow examination; genetic alterations in the tumor cells (eg, del[17p], del[11q], 12q+, immunoglobulin variable region heavy chain mutation analysis); computed tomography scan of neck, chest, abdomen, and pelvis with contrast; and patient-reported outcomes (European quality of life 5-dimensions 5-levels health questionnaire [EQ-5D-5L] and European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire [EORTC QLQ-C30]).

Imaging of the neck, chest, abdomen, and pelvis by computed tomography with contrast will be performed at Screening, at Cycle 4, then every 3 cycles for 25 cycles, followed by every 6 cycles (± 14 days) thereafter, until disease progression, death, lost to follow-up, withdrawal of consent, or end of study, whichever occurs first (as described in Section 5.5.3).

Patients with a potential complete response or complete response with incomplete bone marrow recovery will undergo a bone marrow examination to confirm complete response or complete response with incomplete bone marrow recovery, and possibly to determine the presence or absence of [redacted] (as described in Section 5.5.4).

Patients should remain on study treatment until disease progression is confirmed by independent central review.

[redacted]

Assessments of safety will include adverse events (AEs), serious adverse events , clinical laboratory tests, physical examinations, electrocardiograms, and vital signs. Adverse events will be graded for severity per the current version of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. An independent Data Monitoring Committee will periodically monitor safety data and also perform the interim efficacy analysis.

Key Eligibility Criteria:

The patients to be included in this trial will have a confirmed diagnosis of CLL or SLL that meets the International Workshop on Chronic Lymphocytic Leukemia criteria and requiring treatment as defined by at least 1 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 18 years or older, relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL, with the last dose of prior therapy for CLL/SLL > 14 days before randomization, and have measurable disease (defined as ≥ 1 lymph node > 1.5 cm in longest diameter, and measurable in 2 perpendicular diameters). Note: A line of therapy is defined as completing at least 2 cycles of treatment of standard regimen according to current guidelines, or of an investigational regimen on a clinical trial. Patients will have no history of prolymphocytic leukemia or Richter's transformation, no currently active clinically significant cardiovascular disease, and no active infection with hepatitis B or C or HIV.

Test Product, Dose, and Mode of Administration:

Zanubrutinib (160 mg twice daily) will be administered orally.

Reference Therapy, Dose, and Mode of Administration:

Ibrutinib (420 mg once daily) will be administered orally.

Statistical Methods:

Efficacy Analyses

The primary analysis set for all efficacy analyses is the Intent-to-Treat Analysis Set (all patients randomized). For the non-inferiority testing for the primary endpoint of ORR by independent central review, the analysis will also be performed using the Per-protocol Analysis Set.

Primary Efficacy Endpoint Analysis:

The primary efficacy analysis of ORR (PR or higher, defined as CR/CR with incomplete bone marrow recovery + PR + nodular PR)) will be conducted as assessed by independent central review, using the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2008), with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2) and per Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) for patients with SLL (Appendix 3).

The primary hypothesis testing for ORR by independent central review is for non-inferiority. The non-inferiority of zanubrutinib to ibrutinib will be tested for the Intent-to-Treat Analysis Set under the pre-specified margin of 0.8558 (response ratio of zanubrutinib to ibrutinib). The primary objective of

the study is met if the non-inferiority is demonstrated. The null and alternative hypotheses for testing ORR non-inferiority are as follows:

- H_{0NI}: Response Ratio (zanubrutinib/ibrutinib) ≤ 0.8558
- H_{aNI}: Response Ratio (zanubrutinib/ibrutinib) > 0.8558

There will be 1 interim analysis approximately 12 months after 268 patients (67% information fraction) have been randomized. The final analysis will occur approximately 12 months after 400 patients have been randomized. Based on the assumption to randomize 400 patients in 17 months, the final analysis is expected to occur [redacted] months after the study start.

A Cochran-Mantel-Haenszel test for response ratio adjusting for the 4 randomization stratification factors will be performed for hypothesis testing. The Cochran-Mantel-Haenszel response ratio will be estimated along with its 95% Wald confidence interval (CI). Clopper-Pearson 95% CI will be calculated for ORR for each treatment group.

If non-inferiority is demonstrated at either interim or final analysis, superiority of zanubrutinib to ibrutinib will be tested next (Brannath et al 2003). The monitoring boundaries for the non-inferiority and superiority tests are based on O'Brien Fleming type alpha spending function and depicted in Table 5 and Table 6. The p-value will be used for the primary inference.

Justification of Non-inferiority Margin

The non-inferiority margin was derived using the 95%-95% fixed margin method (FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness 2016). The efficacy of ibrutinib (M1) in response ratio scale was estimated as 2.1781 from the results of RESONATE and RESONATE2 trials by a fixed-effect meta-analysis. Requiring 80% of M1 to be retained in zanubrutinib, a non-inferiority margin of 0.8558 is generated. The margin is within the clinically acceptable limit.

Secondary Efficacy Endpoint Analyses

Key secondary efficacy endpoint

If the primary objective of demonstrating non-inferiority of zanubrutinib to ibrutinib in ORR by independent central review is met, the key secondary efficacy endpoint of progression-free survival (PFS) by independent central review will be tested for non-inferiority under hierarchical testing to control study-wide type I error. There will be 2 analyses for the PFS non-inferiority – an interim analysis at the final ORR analysis time (93 PFS events expected) and a final analysis (205 PFS events).

PFS by independent central review will be compared between the 2 arms using a stratified log-rank test based on the 4 randomization stratification factors. The non-inferiority margin for the test is 1.3319 in hazard ratio (HR; zanubrutinib/ibrutinib). If the p-value from the stratified log-rank test for non-inferiority testing meets the monitoring boundary (Section 9.2.6.2) at either interim or final analysis, the non-inferiority of zanubrutinib to ibrutinib in PFS by independent central review is demonstrated, and further testing of superiority will be performed. The HR (zanubrutinib/ibrutinib) and its 95% CI will be estimated from a stratified Cox regression model. The distribution of PFS, including median and other quartiles, and PFS rate at selected timepoints will be estimated using the Kaplan-Meier method for each arm.

Other secondary efficacy endpoints:

No hypothesis testing will be performed for other secondary efficacy endpoints.

- The HR for PFS by investigator assessment and its 95% CI will be estimated from a stratified Cox regression using the four randomization stratification factors. Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group.

- The distribution of DOR by independent central review including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group. The same analysis will be performed for DOR by investigator assessment.
- The HR for time to treatment failure and its 95% CI will be estimated from a stratified Cox regression using the 4 randomization stratification factors. Kaplan-Meier method will be used to estimate the distribution of time to treatment failure for each treatment group.
- Rate of response for partial response with lymphocytosis or higher by independent central review will be analyzed using the Cochran-Mantel-Haenszel response ratio along with its 95% Wald CI. Clopper-Pearson 95% CI for the estimate will be calculated for each treatment group.
- Overall survival will be analyzed using the same methods employed for PFS by investigator assessment.
- Patient-reported outcomes: The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint for each treatment group. Change of EQ-5D-5L score will be summarized for each treatment group.

Safety Analyses

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

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

All treatment-emergent Aes will be summarized. Serious adverse events, 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.

Sample Size Considerations

The sample size calculation is based on the primary efficacy analyses for the primary endpoint of ORR by independent central review. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.25 (75%/60%), 400 patients will provide more than 99% power to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio) and a 1-sided alpha level of 0.025 when there is 1 interim analysis at 67% information fraction (268 out of 400 patients). Four hundred (400) patients will provide 88% power to demonstrate superiority at a 1-sided alpha level of 0.025 under the alternative hypothesis (response ratio = 1.25) when there is 1 interim analysis at 67% information fraction.

If the primary objective of non-inferiority of ORR is met, the study will continue until 205 PFS events have occurred. At a 1-sided alpha of 0.025 and a non-inferiority margin of 1.3319 (HR), the power to demonstrate the non-inferiority of zanubritinib to ibrutinib in PFS by independent central review is 80% with 1 interim analysis expected at the time of the ORR final analysis. [redacted] A median PFS of [redacted] months for ibrutinib, an HR of 0.9, and an exponential distribution for PFS are also assumed.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BTK	Bruton tyrosine kinase
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CT	computed tomography
CYP	cytochrome P450
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire
EQ-5D-5L	European quality of life 5-dimensions 5-levels health questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
IC_{50}	inhibitory concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IGHV	immunoglobulin variable region heavy chain
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
Pi3K	phosphatidyl inositol 3-kinase
[redacted]	[redacted]
PR	partial response
PR-L	partial response with lymphocytosis
PRO	patient-reported outcome
R/R	relapsed/refractory
SAE	serious adverse event
SLL	small lymphocytic lymphoma
zanubrutinib	BGB-3111

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 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 a treatable but essentially incurable disease. Diagnosis of CLL requires the presence of ≥ 5000 B lymphocytes/µL in the peripheral blood for at least 3 months with clonality of the circulating B lymphocytes confirmed by flow cytometry. The leukemia cells are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Presence of a cytopenia caused by a typical marrow infiltrate defines the diagnosis of CLL regardless of the number of peripheral blood B lymphocytes or lymph node involvement. Diagnosis of SLL requires the presence of lymphadenopathy and absence of cytopenia caused by a clonal marrow infiltrate. The number of B lymphocytes in the peripheral blood should also not exceed 5000/µL for SLL. CLL cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin are characteristically low compared to those found on normal B cells, with each clone of leukemia cells restricted to expressing either kappa or lambda immunoglobulin light chains (Moreau et al 1997; Ginaldi et al 1998; Hallek 2017).

Genomic landscaping of CLL has revealed that the disease may often be initiated by the loss or addition of large chromosomal elements, eg, deletion 13q (~ 55%), deletion 11q (~ 25%), or trisomy 12 (10% to 20%), followed by additional mutations that may render the leukemia more aggressive (Landau et al 2015). Deletions of the short arm of chromosome 17 (del[17p]) are detected in 5% to 8% of chemotherapy-naïve patients and almost always include band 17p13 where the tumor suppressor gene TP53 is located. Patients with the del[17p] clone tend to show marked resistance against genotoxic chemotherapies that cannot be overcome by the addition of anti-CD20 antibodies (Hallek et al 2010; Seiffert et al 2012). In addition to these mutations, additional recurrently mutated genes and somatic copy number variations have also been identified including NOTCH1, MYD88, TP53, ATM, SF3B1, FBXW7, POT1, CHD2, RPS15, IKZF3, ZNF292, ZMYM3, ARID1A, and PTPN11 (Landau et al 2015; Quesada et al 2011; Puente et al 2011; Puente et al 2015).

Survival of CLL cells is dependent on a permissive microenvironment composed of macrophages, T cells, or stromal follicular dendritic cells providing stimuli for activation of crucial survival and pro-proliferative signaling pathways in transformed cells (Tsukada et al 2002; Pedersen et al 2002; Burger et al 2009; Hallek 2017). This microenvironment produces chemokines, cytokines, and angiogenic factors that can interact with the leukemia cells, providing support for their survival (Burger et al 2009; Chiorazzi et al 2005; Reinart et al 2013; Hallek 2017).

Staging of CLL is typically per either the modified Rai or Binet staging system. Modified Rai defines low-risk disease as those with lymphocytosis with circulating leukemia cells and/or marrow involvement (lymphoid cells > 30%) (formerly Rai stage 0). Patients with lymphocytosis, lymphadenopathy, splenomegaly, and/or hepatomegaly are categorized as intermediate-risk disease (formerly Rai stage I or II), whereas high-risk disease includes patients with disease-related anemia (hemoglobin [Hgb] < 11 g/dL) and/or thrombocytopenia (platelet count < 100 x 10^9/L) (formerly Rai stage III and formerly Rai stage IV, respectively) (Rai et al 1975). The Binet staging system is based on the number of areas involved, ie, presence of enlarged lymph nodes, organomegaly, or whether there is anemia or thrombocytopenia. Areas of involvement considered include head and neck (including Waldeyer ring), axillae, groins, spleen, and liver. Binet defines stage A as Hgb ≥ 10 g/dL, platelet count ≥ 100 x 10^9/L, and up to 2 involved areas; stage B is Hgb ≥ 10 g/dL, platelet count ≥ 100 x 10^9/L, and organomegaly greater than that defined for stage A (3 or more areas of nodal or organ enlargement); stage C is Hgb < 10 g/dL and/or platelet count < 100 x 10^9/L (Binet et al 1981).

Decision to initiate treatment for CLL/SLL is based upon the presence of progressive or active/symptomatic disease, eg, progressive marrow failure, massive or progressive splenomegaly and/or lymphadenopathy, worsening lymphocytosis with an increase of > 50% over a 2-month period, lymphocyte doubling time of < 6 months, autoimmune complications that respond poorly to corticosteroids or other standard therapies, and/or constitutional symptoms (Hallek et al 2008).

Front-line CLL treatment for those without del[17p] or TP53 mutations may include combination fludarabine, cyclophosphamide, and rituximab, or bendamustine and rituximab for the frail elderly patients, while for those with del[17p] or TP53 mutations, ibrutinib (Bruton tyrosine kinase [BTK] inhibitor) or idelalisib (phosphatidyl inositol 3-kinase [Pi3K] delta inhibitor) plus rituximab should be considered. For patients with impaired physical condition such as those with abnormal creatinine clearance and/or a low cumulative illness rating scale score but without del[17p] or TP53 mutations, treatment with chlorambucil + an anti-CD20 antibody such as obinutuzumab, or single-agent ibrutinib, may be considered. For those with impaired physical condition who have del[17p] or TP53 mutations, single-agent ibrutinib, alemtuzumab, high-dose rituximab, or ofatumumab would be the preferred treatment options (Bauer et al 2012; Goede et al 2015; Hillmen et al 2015; Hallek 2017; Robak et al 2010).

Second-line treatment for refractory CLL, defined as disease relapse within 6 months after last treatment, or for disease that relapses within 3 years after first remission, may include ibrutinib, idelalisib plus rituximab, venetoclax (BH3-mimetic designed to block the function of the Bcl-2 protein) alone or in combination with an anti-CD20 antibody; alemtuzumab; fludarabine, cyclophosphamide, and rituximab (after bendamustine and rituximab) and vice versa; or lenalidomide. For the suitable patient, allogeneic stem cell transplantation may also be offered. For patients who progress after 3 years from initial remission, the same first-line therapy may be administered again.

1.2 B-cell Receptor Signaling

B-cell receptor signaling is an important component for the survival of CLL cells, with continuous or repetitive B-cell receptor signaling capable of enabling the growth of CLL cells (Petlickovski et al 2005; Stevenson et al 2011). The B-cell receptor signaling in CLL cells is supported by different tyrosine kinases including BTK, spleen tyrosine kinase, ZAP70, Src family kinases, and Pi3K.

Blockade of the B-cell receptor signaling cascade by inhibition of either BTK (Honigberg et al 2010) or the delta isoform of Pi3K (Zelenetz et al 2017) has been shown to induce profound inhibition of proliferative signaling from CLL cell-host interactions, resulting in frequent and durable responses in patients with both previously untreated and relapsed/refractory (R/R) CLL. While the use of Pi3K delta inhibitors is often limited by toxicities including hepatotoxicity, colitis, and infection complications, particularly when used in combination with other agents (Zydelig® Summary of Product Characteristics) and in previously untreated patients (Falchi et al 2016), the BTK inhibitor ibrutinib has a highly favorable tolerability profile when compared to conventional therapies.

1.2.1 Ibrutinib

Ibrutinib is a small-molecule inhibitor of BTK. Nonclinical studies have demonstrated inhibition of malignant B-cell proliferation and survival by ibrutinib in vivo, as well as cell migration and substrate adhesion in vitro. In patients with recurrent B-cell lymphoma, > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In a Phase 1b/2 study of patients with R/R CLL (n = 85) where 51 patients received ibrutinib at a daily dose of 420 mg and 34 patients received ibrutinib at a daily dose of 840 mg, the overall response rate (ORR) was identical at 71% for both groups of patients. An additional 20% and 15% of patients had partial response (PR) with lymphocytosis (PR-L) in the 2 groups, respectively. The responses observed were independent of clinical and genomic risk factors including del[17p]. At 26 months, the estimated progression-free survival (PFS) rate was 75%, and the overall survival (OS) rate was 83% (Byrd et al 2013). In another Phase 1b/2 trial that evaluated the combination of ibrutinib with ofatumumab in patients with either R/R CLL/SLL, prolymphocytic leukemia, or Richter's transformation who had failed at least 2 prior therapies, ORR for patients with CLL/SLL was 100%, with estimated 12-month PFS of 89% (Jaglowski et al 2015).

In a Phase 3 study that compared ibrutinib to ofatumumab in patients with relapsed or refractory CLL (RESONATE), at median follow-up of 9.4 months, ibrutinib was found to significantly improve PFS compared to ofatumumab (ibrutinib: median duration not reached; ofatumumab: 8.1 months; $p < 0.001$). Ibrutinib also significantly improved OS, with an OS rate of 90% at 12 months for ibrutinib versus 81% for ofatumumab ($p = 0.005$).

Overall response rate, per independent central review, was 42.6% (PR: 42.6%) for ibrutinib versus 4% (PR: 4%) for ofatumumab; PR-L rate was 20% and 0% for the 2 treatment groups, respectively.

Overall response rate, per investigator review, was 69.7% (complete response [CR]/complete response with incomplete bone marrow recovery [CRi]: 2%; PR: 68%) for ibrutinib versus 21.4% (CR/CRi: 1%; PR: 21%) for ofatumumab; PR-L rate was 15% and 2% for the 2 treatment groups, respectively.

In another Phase 3 study (HELIOS) that compared 6 courses of bendamustine and rituximab in combination with either ibrutinib or placebo (n = 578) in patients with R/R CLL, at a median follow-up of 17 months, PFS was significantly improved in the ibrutinib group (not reached) versus placebo (13.3 months) ($p < 0.0001$) (Chanan-Khan et al 2016).

Ibrutinib is well tolerated compared with chemotherapeutic treatments for CLL. In the Phase 3 RESONATE study, Grade 3 or higher adverse reactions reported in ≥ 10% of patients treated with ibrutinib were diarrhea (4%), nausea (2%), stomatitis (1%), pyrexia (2%), upper respiratory tract infection (1%), pneumonia (10%), sinusitis (1%), urinary tract infection (4%), rash (3%), musculoskeletal pain (2%), arthralgia (1%), headache (1%), neutrophils decreased (23%), and platelets decreased (5%). For the Phase 3 study comparing ibrutinib to chlorambucil in patients with CLL (RESONATE2), Grade 3 or higher adverse reactions reported in ≥ 10% of patients treated with ibrutinib were diarrhea (4%), stomatitis (1%), musculoskeletal pain (4%), arthralgia (1%), rash (4%), skin infection (2%), pneumonia (8%), urinary tract infections (1%), peripheral edema (1%), hypertension (4%), and headache (1%). Across clinical trials, Grade 3 or higher bleeding events occurred in up to 6% of patients treated with ibrutinib, with bleeding event of any grade including bruising and petechiae occurring in approximately 50% of patients. Atrial fibrillation and atrial flutter occurred in 6% to 9% of patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infection, and a prior history of atrial fibrillation. Other malignancies (3% to 16%) including non-skin carcinomas (1% to 4%) have been observed in patients on ibrutinib. Tumor lysis syndrome has infrequently been reported with ibrutinib therapy. Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman (Imbruvica® US Prescribing Information).

Ibrutinib is currently approved by the United States Food and Drug Administration (FDA) for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy, patients with CLL/SLL with or without 17p deletion, patients with Waldenström macroglobulinemia, patients with marginal zone lymphoma who have received at least 1 prior anti-CD20 based therapy, and patients with chronic graft versus host disease after failure of 1 or more lines of systemic therapy (Imbruvica® US Prescribing Information).

1.2.2 Zanubrutinib

Zanubrutinib (also known as BGB-3111) is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacologic and pharmacokinetic (PK) profile. Zanubrutinib is different from ibrutinib in the following ways:

1. Zanubrutinib is more selective 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 anti-tumor effects of rituximab.

1.2.2.1 Nonclinical Data for Zanubrutinib

Summaries of nonclinical studies are provided below. [redacted]

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 phospholipase C gamma 2 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 to 20 nM, while it was inactive in many other hematologic cancer cell lines.

In vivo studies have demonstrated that zanubrutinib induces dose-dependent anti-tumor 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 anti-tumor activity than ibrutinib in a TMD-8 diffuse large B-cell lymphoma subcutaneous xenograft model. In a PK/pharmacodynamics 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, 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.

Cytochrome P450 (CYP) phenotyping in human liver microsomes suggests that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism. Based on in vitro data, zanubrutinib has the potential to be a moderate inhibitor for CYP2C8 (IC_{50} = 4.03 μM), CYP2C9 (IC_{50} = 5.69 μM), and CYP2C19 (IC_{50} = 7.80 μM), while the IC_{50}s for other CYP isozymes were all > 10 μM. Zanubrutinib is not a time-dependent CYP inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Drug-drug interactions between zanubrutinib and CYP2C8, CYP2C9, and CYP2C19 substrates would be dependent on final plasma levels obtained in humans at therapeutic doses. Zanubrutinib has weak CYP3A induction potential at concentration ≥ 3 μM in primary human hepatocytes.

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 corrected QT interval (QTc) changes were noted in the conscious telemetry-implanted dogs over 24 hours after dosing up to 100 mg/kg, or in the repeat dose toxicity studies in dogs over 91 days at doses up to 100 mg/kg/day. No mortality or severe toxicity was noted in 91-day repeat dose toxicity studies in both rats and dogs at doses up to 300 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.

1.2.2.2 Summary of Relevant Clinical Experience with Zanubrutinib

Dose Selection for Zanubrutinib

In the first-in-human, Phase 1 study, BGB-3111-AU-003, the PK of zanubrutinib was linear between 40 and 320 mg orally once daily [redacted] 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 daily. Results from a food effect study showed that zanubrutinib exposure was not altered by a 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 daily 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, Waldenström 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 daily and 320 mg once daily 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 daily has been selected as the recommended Phase 3 dose based on sustained target occupancy, high rates of objective response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

Preliminary Efficacy and Safety Data for Zanubrutinib

As of 31 March 2017, 69 patients with treatment-naïve (n = 16) or R/R (n = 50) CLL were enrolled in the BGB-3111-AU-003 study (first-in-human, Phase 1). Among the 69, 66 patients had at least 12 weeks of follow-up and were evaluable for efficacy. Overall response rate for these 66 patients was 94%, with 3% CR (n = 2), 82% PR (n = 54), and 9% PR-L (n = 6). Stable disease was 5% (n = 3), and 1 subject (2%) discontinued treatment prior to assessment.

For patients with treatment-naïve CLL, ORR was 100% with 6% CR (n = 1), 81% PR (n = 13), and 13% PR-L (n = 2); whereas for patients with R/R CLL/SLL, ORR was 92% with 2% CR (n = 1), 82% PR (n = 41), and 8% PR-L (n = 4). Overall response rate for patients with del[17p] and/or del[11q] was 96%. Adverse events (AEs) reported in > 10% of patients, independent of causality, were petechiae/purpura/contusion (46%), fatigue (29%), upper respiratory tract infection (28%), cough (23%), diarrhea (22%), headache (19%), hematuria (15%), nausea (13%), rash (13%), arthralgia (12%), muscle spasms (12%), and urinary tract infection (12%). There was 1 patient among 69 evaluable patients who had experienced a Grade 3 or higher AE of petechiae/purpura/contusion). For Adverse Event of Interest, there were 1 AE of Grade 2 atrial fibrillation (1%), 1 serious adverse event (SAE) of Grade 2 diarrhea (1%), and 1 SAE of Grade 3 purpura (subcutaneous hemorrhage) (1%); none of which led to treatment discontinuation.

1.2.2.3 Benefit-Risk Assessment

Approximately [redacted] patients have been enrolled worldwide in completed and ongoing clinical trials evaluating zanubrutinib and have received at least 1 dose of zanubrutinib; of these, [redacted] patients have been treated with zanubrutinib monotherapy. Available data for zanubrutinib in patients with CLL/SLL support a positive benefit-risk profile for the use of zanubrutinib as an investigational agent for treatment of CLL/SLL.

2 STUDY OBJECTIVES

Primary:

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by overall response rate determined by independent central review

Secondary:

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
  - Progression-free survival determined by independent central review
  - Progression-free survival determined by investigator assessment
  - Duration of response as determined by independent central review
  - Duration of response as determined by investigator assessment
  - Time to treatment failure
  - Rate of partial response with lymphocytosis or higher determined by independent central review
  - Overall survival
  - Patient-reported outcomes
- To compare the safety of zanubrutinib versus ibrutinib

Exploratory:

- [redacted]

3 STUDY DESIGN

3.1 Summary of Study Design

This is a Phase 3, randomized study of zanubrutinib versus ibrutinib in approximately 400 patients with R/R CLL/SLL. Refractory disease is defined as either no objective response to or disease progression within 6 months of the last treatment, and relapsed disease is defined as patients whose disease relapses more than 6 months after the last treatment and subsequently progressed. The primary efficacy endpoint is ORR determined by independent central review. Disease response will be assessed per the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2), and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL (Appendix 3). Rate of PR-L or higher will be assessed as a secondary efficacy endpoint considering the finding that treatment with BTK inhibitors may lead to lymphocytosis due to redistribution of leukemia cells from lymphoid compartment to blood. In these instances, treatment-related transient progressive lymphocytosis is not a sign of treatment failure or disease progression and has no bearing on treatment outcome (Woyach et al 2014).

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del[17p]/TP53 mutation status (present or absent). [redacted]

Treatment with zanubrutinib and ibrutinib will be open label. Study treatment must commence within 5 days after randomization/treatment assignment and will be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination. Each cycle consists of 28 days. [redacted]

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; laboratory studies; bone marrow examination, genetic alterations in the tumor cells (including del[17p], del[11q], 12q+, and immunoglobulin variable region heavy chain [IGHV] mutation analysis); computed tomography (CT) scan of neck, chest, abdomen, and pelvis with contrast; and patient-reported outcomes (PROs; European quality of life 5-dimensions 5-levels health questionnaire [EQ-5D-5L] and European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire [EORTC QLQ-C30]).

Imaging of the neck, chest, abdomen, and pelvis and any other disease sites by CT with contrast will be performed as indicated in Appendix 12 until disease progression, death, lost to follow-up, withdrawal of consent, or end of study, whichever occurs first (as described in Section 5.5.3).

Patients with a potential CR or CRi will undergo a bone marrow examination to confirm CR or CRi, [redacted]

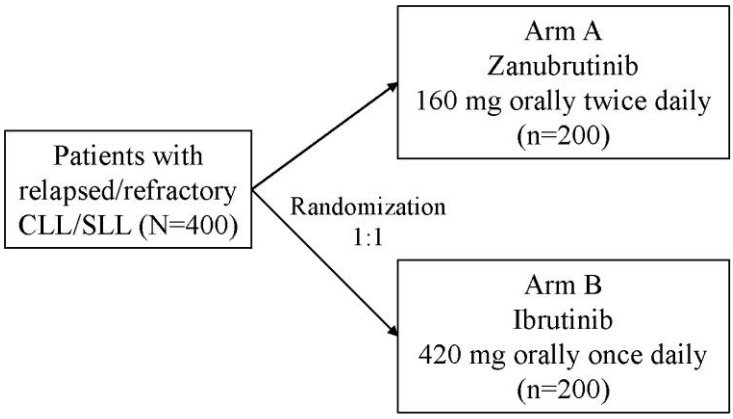
Patients should remain on study treatment until disease progression is confirmed by independent central review (as described in Section 6.6).

[redacted]

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, electrocardiogram (ECG), and vital signs. AEs will be graded for severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. An independent Data Monitoring Committee (DMC) will periodically monitor safety data.

3.2 Study Schema

Figure 1. Study Schema



Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del[17p]/TP53 mutation status (present versus absent).

3.3 Blinding

Treatment with zanubrutinib and treatment with ibrutinib will be open label; however, the assessment of ORR by independent central review (primary endpoint) will be blinded.

3.4 Study Rationale

B-cell receptor signaling regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival (Advani et al 2013). It also plays an important role in survival of CLL cells. BTK has a relevant role in the signal transduction of B-cell receptor and can lead to downstream activation of cell survival pathways such as NF-κB and MAP kinases via the Src family kinases. Ibrutinib, an FDA-approved first-generation BTK inhibitor that blocks B-cell receptor signaling in human B cells via specific active site occupancy, has been shown to be efficacious and tolerated in the treatment of CLL/SLL.

In the Phase 3 RESONATE study that compared ibrutinib to ofatumumab in patients with relapsed or refractory CLL/SLL, ORR (PR or higher) per independent central review was 42.6% (PR: 42.6%) for ibrutinib, whereas per investigator review, ORR was 69.7% (CR/CRi: 2%; PR: 68%) for ibrutinib (Byrd et al 2014). Across ibrutinib clinical trials, Grade 3 or higher bleeding events occurred in up to 6% of patients treated with ibrutinib, with bleeding event of any grade including bruising and petechiae occurring in approximately 50% of patients. Atrial fibrillation and atrial flutter occurred in 6% to 9% of patients treated with ibrutinib (Imbruvica® U.S. Prescribing Information).

As of 31 March 2017, preliminary efficacy data from the Phase 1 BGB-3111-AU-003 revealed a response rate per protocol definition (CR/CRi + PR + PR-L) of 92% for patients with R/R CLL,

with 2% CR (n = 1), 82% PR (n = 41), and 8% PR-L (n = 4). Response rate for PR or higher was 84% in the R/R population.

Treatment with zanubrutinib has been well tolerated across all studies thus far. Compared to ibrutinib, zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, henceforth possibly leading to reduced toxicities due to off-target inhibition such as diarrhea, thrombocytopenia, bleed, atrial fibrillation, rash, and fatigue. In study BGB-3111-AU-003, there was 1 patient among 69 evaluable patients who had experienced a Grade 3 or higher AE of petechiae/purpura/contusion. In terms of Adverse Event of Interest, atrial fibrillation was reported in 1 patient (1%), an SAE of Grade 2 diarrhea in 1 patient, and an SAE of purpura (subcutaneous hemorrhage) in 1 patient; none of which led to treatment discontinuation. No event of Richter's transformation has occurred.

Based on the preliminary data from BGB-3111-AU-03, the efficacy of zanubrutinib in the treatment of CLL/SLL (PR or higher: 84%) is hypothesized to at least be non-inferior to ibrutinib (PR or higher [RESONATE]: 69.7% per investigator review; 42.6% per independent central review). Preliminary safety data from the BGB-3111-AU-03 study also revealed a tolerable and safe profile for zanubrutinib, with possibly a lower rate of Adverse Event of Interest such as atrial fibrillation and bleed when compared with ibrutinib. In view of these findings, a Phase 3 non-inferiority study comparing the efficacy of zanubrutinib and ibrutinib measured by ORR, the primary endpoint, will be conducted.

3.5 Duration of Study

[redacted] Patients receiving zanubrutinib, who in the opinion of the investigator, continue to benefit from study treatment may continue treatment with zanubrutinib by enrolling on the Zanubrutinib Long Term Extension Study. This study is a rollover study for patients who wish to continue receiving zanubrutinib.

4 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

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

1. Age 18 years or older
2. Confirmed diagnosis of CLL or SLL that meets the IWCLL criteria (Hallek et al 2008)
3. CLL/SLL requiring treatment as defined by at least 1 of the following criteria:
    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 x 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. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy

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)

   iii. Fevers > 100.5ºF or 38ºC for ≥ 2 weeks without other evidence of infection

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

4. Relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL. A line of therapy is defined as completing at least 2 cycles of treatment of standard regimen according to current guidelines or of an investigational regimen on a clinical trial

5. Measurable disease by CT/magnetic resonance imaging (MRI). Measurable disease is defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

7. Life expectancy ≥ 6 months

8. Adequate bone marrow function as defined by:

   a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 (growth factor use is allowed), except for patients with bone marrow involvement in which case ANC must be ≥ 750/mm^3

   b. Platelet ≥ 75,000/mm^3 (may be post-transfusion), except for patients with bone marrow involvement by CLL in which case the platelet count must be ≥ 50,000/mm^3

9. 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/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 2.5 × upper limit of

normal unless due to CLL/SLL

c. Serum total bilirubin < 2.0 × upper limit of normal (unless documented Gilbert's syndrome)

10. Female patients of childbearing potential must practice highly effective methods (Section 5.1.2) of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
11. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception with other highly effective methods described in Section 5.1.2 during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
12. Ability to provide written informed consent and can understand and comply with the requirements of the study.

4.2 Exclusion Criteria

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

1. Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation (biopsy based on clinical suspicion may be needed to rule out transformation)
2. 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 (Appendix 4)
   d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes)
   e. QTcF > 480 milliseconds based on Fridericia's formula
   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 mmHg and diastolic blood pressure > 105 mmHg at screening
3. Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast
4. 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
5. History of stroke or intracranial hemorrhage within 180 days before first dose of study drug
6. Severe or debilitating pulmonary disease

7. 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
8. Active fungal, bacterial, and/or viral infection requiring systemic therapy
9. Known central nervous system involvement by leukemia or lymphoma
10. 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
11. Known infection with HIV or serologic status reflecting active viral hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antibody (HBsAb) 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 (< 20 IU), and if they are willing to undergo monthly monitoring for HBV reactivation
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable
12. Moderate or severe hepatic impairment, ie, Child-Pugh class B or C
13. Major surgery within 4 weeks of the first dose of study drug
14. Prior treatment with a BTK inhibitor
15. Last dose of prior therapy for CLL/SLL ≤ 14 days before randomization, with the following additional exclusion requirements:
    a. Treatment with monoclonal antibody-based therapy within 28 days of first dose of study drug
    b. Treatment with chimeric antigen receptor T-cell therapy within 180 days of first dose of study drug
    c. Treatment with Chinese herbal medicine with anticancer intent within 28 days of first dose of study drug
    d. Chemotherapy or radiation treatment within 21 days of first dose of study drug or hematopoietic stem cell transplantation within 90 days of first dose of study drug
16. Prior steroid use
    - For prior corticosteroid use of 10mg/day or less, regardless of reason or duration of treatment, must stop steroid no later than day prior to first dose.
    - For prior corticosteroid use of 10mg/day or more, regardless of reason or duration of treatment, must stop steroid 4 weeks prior to date of randomization.
17. Toxicity from prior anticancer therapy that has not recovered to ≤ Grade 1 (except for alopecia, ANC, and platelet count; for ANC and platelet count, see inclusion criterion 8)

18. Pregnant or lactating women
19. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
20. Ongoing alcohol or drug addiction
21. Hypersensitivity to zanubrutinib, ibrutinib, or any of the other ingredients in either drug
22. Patient requires treatment with warfarin or other vitamin K antagonists
23. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
24. Concurrent participation in another therapeutic clinical trial.

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 Schedule of Assessments (Appendix 12).

Visit Windows

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 7 days (ie, 7 days before or after the given day) unless otherwise stated in the Schedule of Assessments. Study drug supplies must be taken into account when scheduling visits during windows. 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

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 (ICF) will be given to the patient to read, and the patient must have adequate time to understand the content 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 Independent Ethics Committee (IEC).

All screening procedures must be performed within 35 days of the first dose of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. Repeating screening procedures or tests are allowed once 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 post-menopausal 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
  - 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 (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- 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 or ibrutinib. 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 postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal 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.

5.1.3 Patient Numbering

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

5.1.4 Medical and Cancer History

Review all medical and cancer history after obtaining informed consent, including presence or absence of disease-related constitutional symptoms. Clinically significant medical history (ie, previous diagnoses, diseases, or surgeries) that does not pertain to the study indication, started before signing the informed consent, but considered relevant to the patient's study eligibility will be collected and captured in the electronic case report form (eCRF). "Clinically significant" is defined as any event, diagnosis, or laboratory value requiring treatment or 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, year of birth [or age], and race/ethnicity) will also be collected.

Record non-serious AEs during the screening period as medical history.

5.1.5 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. No eligibility waiver 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 the medical monitor or designee will provide final approval for enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Authorization Packet is in the patient's file before proceeding with study procedures.

After a patient is randomized, refer to concomitant therapies (Section 7) and study drug discontinuation (Section 6.6) for guidance on a patient's eligibility for treatment.

5.1.6 Enrollment/Randomization

Interactive Response Technology will be used to randomize patients to treatment arm and to dispense study drug. Study treatment must commence within 5 days after randomization.

5.2 Study Drug Dispensation

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

[redacted]

5.4 Safety Assessments

5.4.1 Cardiac Function

An assessment of left ventricular ejection fraction will be performed and documented at Screening and as medically indicated. Note: An echocardiogram, multigated acquisition, and gated heart pool scan are all acceptable.

5.4.2 Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, heart rate, and body temperature), weight, and review for arrhythmia signs/symptoms (eg, shortness of breath, dizziness, or fainting) will be performed at each study visit during study treatment and at the Safety Follow-up Visit. Height (cm) is determined at Screening only.

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

5.4.3 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.

5.4.4 Electrocardiogram

A 12-lead ECG will be performed locally in triplicate at screening for all subjects. During study treatment, ECGs will be performed as specified per the Schedule of Assessments (Appendix 12). Subjects should be in the semi-recumbent or supine position.

5.4.5 Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 35 days before Cycle 1 Day 1, and on study thereafter.

5.4.6 Adverse Events Review

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

Collect non-serious AE information from the time of first dose of study drug through Safety Follow-up. Information on all SAEs (regardless of relatedness) will be collected from the time of signing of informed consent through screen failure or Safety Follow-up. 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, and the definition of an SAE is provided in Section 8.2.1. Important additional requirements for reporting SAEs are explained in Section 8.

In addition, arrhythmia signs/symptoms will be reviewed at every cycle. This will involve the investigators asking subjects for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness, or fainting) as part of the routine AE monitoring for each cycle.

5.5 Efficacy Assessments

Response will be assessed by independent central review and categorized per the "modified" IWCLL criteria (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2), and per the Lugano Classification for NHL (Cheson et al 2014) for patients with SLL using CT-based response criteria (Appendix 3). PD assessed by CT for SLL must be confirmed by repeat imaging no sooner than 4 weeks from the first imaging that shows possible progression to rule out pseudo-progression. Patients may continue study treatment while they wait for the confirmatory imaging. Investigators will also assess response locally. The primary endpoint will be ORR based on independent central review. Refer to Appendix 2 and Appendix 3 for the response parameters. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 12).

5.5.1 Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms based on "modified" IWCLL criteria (Hallek et al 2008) (unexplained fever of $\geq 38^{o}$C; unexplained, recurrent drenching night sweats; or unexplained loss of > 10% body weight within the previous 6 months) will be evaluated as specified per the Schedule of Assessments (Appendix 12).

5.5.2 Examination of Liver, Spleen, and Lymph Nodes

Record presence or absence of hepatomegaly, splenomegaly, and/or lymphadenopathy as specified per the Schedule of Assessments (Appendix 12). PD assessed by physical examination must be confirmed by a CT scan.

5.5.3 Computed Tomography

All patients must have baseline (within 35 days of randomization) CT scan with intravenous and oral contrast of neck, chest, abdomen, and pelvis and any other disease sites.

A MRI may be used in place of CT only for patients who cannot undergo CT due to contrast allergy. In Germany, an MRI may be used in place of CT in all patients. 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.

CT with contrast of neck, chest, abdomen, and pelvis will be performed as specified per the Schedule of Assessments (Appendix 12).

All CT scans, and MRIs obtained during the study, will be collected and reviewed by a central imaging vendor identified for this trial. De-identified copies of all scans and radiology reports (including those from Screening) must be provided to the sponsor or designee (eg, central imaging vendor).

5.5.4 Bone Marrow Examination

Bone marrow biopsy is required during the Screening period. Thereafter, bone marrow examination is required for patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CRi, and need bone marrow examination to confirm CR or CRi [redacted] Patients who are otherwise complete responders, but show bone marrow involvement, should recheck bone marrow as clinically indicated, but at a minimum at least once per year until CR or CRi is confirmed. Patients should also undergo bone marrow biopsy in the setting of progression of cytopenias unrelated to autoimmune cytopenias or study treatment in order to confirm PD. All the bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory.

5.6 Patient-Reported Outcomes

PROs will be administered via electronic computing devices and continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedule of Assessments (Appendix 12) before study drug is administered and prior to performing any other procedures.

5.6.1 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The EuroQol 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.

5.6.2 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 3000 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 NHL 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.

5.7 Laboratory Assessments

Samples for protocol-specified complete blood count (CBC) will be evaluated by a central laboratory. Additional laboratory assessments, including chemistry and coagulation profiles, laboratory values required within a short time frame on dosing days to determine drug dosage, and unscheduled laboratory tests ordered by the investigator as necessary for patient monitoring, will be performed locally and entered into the eCRF. Samples for serum immunoglobulins, pregnancy testing, and viral hepatitis B and C testing will be performed locally.

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

Laboratory assessments will be performed at the timepoints specified in the Schedule of Assessments (Appendix 12) and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first study drug administration.

5.7.1 Hematology

CBC with differential includes Hgb, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil).

5.7.2 Chemistry

Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, total bilirubin, total protein, albumin, ALT, aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase.

The following 2 chemistry tests will only be done at Screening and will be performed locally: direct antiglobulin test and β-2 microglobulin.

5.7.3 Serum Immunoglobulins

Quantitative serum immunoglobulins (IgG, IgM, and IgA) will be measured.

5.7.4 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 and as clinically indicated.

5.7.5 Hepatitis B and C testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. 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 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 who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo at least monthly HBV DNA screening by PCR. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days.

If, during monthly monitoring of HBV DNA by PCR, the value is between 20 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 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 or continued. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. 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, physicians with expertise in managing hepatitis C.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation. Table 1 describes how the results for HBV and HCV testing at screening relate to study eligibility

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 monthly monitoring of HBV DNA*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not detected"* *Perform monthly monitoring of HCV RNA*	**Antibody (+)** *HCV RNA detected*

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

5.7.6 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. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Day 1 of every cycle and for at least 90 days after the last dose of study drug. 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 participation in the study.

5.8 Biomarkers

CLL/SLL is characterized by various mutations shown to be linked to favorable prognosis (del[13q] and hypermutation of IGHV) or poor prognosis (del[17p], del[11q], unmutated IGHV, mutations in TP53, ATM, and Notch1). All patients will provide blood samples at the time of Screening for assessment of chromosomal abnormalities (del[17p], del[11q], and the marker D13S319 on chromosome 13q, and to determine trisomy 12 by fluorescence in situ hybridization and the mutation status of relevant genes [including but not limited to TP53]) using a specialized central laboratory. IGHV mutational status will also be determined by molecular techniques using blood in a specialized testing laboratory.

[redacted]

[redacted]

5.9 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; and hematology and chemistry laboratory assessments. 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.

5.10 End of Treatment Period

The treatment period starts with the first day of assigned study treatment and continues as defined below by study arm:

- Arm A: The treatment period ends 30 days following date of permanent study drug discontinuation (ie, 30 days after the final administered dose of zanubrutinib)
- Arm B: The treatment period ends 30 days following date of permanent study drug discontinuation (ie, 30 days after the final administered dose of ibrutinib)

Patients may discontinue study drug for any 1 of the reasons presented in Section 6.6.

Patients may voluntarily withdraw consent for treatment at any time.

5.11 Safety Follow-up

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 investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information. Refer to the Schedule of Assessments (Appendix 12) for the assessments to be performed at the Safety Follow-up Visit.

5.12 Long-term Follow-up

All patients who discontinue study drug treatment will remain in the study and subsequently commence Long-term Follow-up, which includes monitoring survival status and subsequent

therapies for CLL/SLL. For patients who permanently discontinue study drug treatment before radiographic progression is documented and confirmed by independent central review, tumor assessments (including radiographic imaging) will continue until radiographic progression is identified and confirmed by independent central review. Refer to the Schedule of Assessments (Appendix 12) for the assessments to be performed at the Long-term Follow-up Visits.

If the patient refuses to return for these visits or is unable to do so, every effort should be made to contact him/her or the patient's guardian by telephone to determine the patient's disease status and survival.

5.13 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

The patient may elect to withdraw from the study for reasons other than those listed above - any other reasons need to be documented and explained in the eCRF. Patients may voluntarily withdraw consent from the study at any time.

5.14 Lost to Follow-up

Every reasonable effort should be made to contact any patient 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 to establish contact fail, 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

The capsule supplied for both zanubrutinib and ibrutinib will be provided in a child-resistant high-density polyethylene bottle with induction seal and bottle label. The label will include, at a minimum, drug name, dose strength, contents, sponsor, protocol number, bottle number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator.

Ibrutinib will be sourced from commercial supplies. The labels will include any additional clinical requirements as appropriate. Refer to the Pharmacy Manual for specifics on packaging and label content.

The contents of the label will be in accordance with all applicable local regulatory requirements.

6.1.2 Handling and Storage

The Interactive Response Technology 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 (59ºF to 86ºF).

The preferred storage condition for ibrutinib will be room temperature 20ºC to 25ºC; however, each site should follow the storage condition instructions on the local drug label. Retain in original package until dispensing.

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).

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.

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. 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, the amount supplied, and/or the amount 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

Zanubrutinib will be dispensed by the study center personnel to patients at study visits 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 approximately 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 dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

Zanubrutinib 160 mg will be taken 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. In case of dose reduction (See Section 6.5.1), the number of capsules taken at each administration will be reduced.

Patients randomized to Arm A (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.

[redacted]

6.2.2 Ibrutinib

Patients randomized to Arm B will receive ibrutinib. Ibrutinib will be administered at a dose of 420 mg orally once daily. Patients will take ibrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Ibrutinib capsules should not be opened, broken, or chewed at any time. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with return to the normal schedule the following day. Extra doses of ibrutinib should not be taken to make up for the missed dose. If a patient vomits after taking the ibrutinib capsules, that dose should not be repeated.

6.3 Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any AE or SAE criterion must be reported in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for zanubrutinib or ibrutinib. 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 ibrutinib, refer to the prescribing information (Imbruvica® US Prescribing Information).

6.4.1 Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment with zanubrutinib or ibrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding.

6.5 Dose Interruption and Modification

6.5.1 Zanubrutinib

The guidelines below should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.5.1.1) and non-hematologic (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) (Section 6.5.1.2) toxicities.

Table 2. Zanubrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Zanubrutinib dose (Arm A)
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
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

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 medical monitor.

6.5.1.1 Zanubrutinib Dose Reduction for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting > 10 days)
- Grade 4 thrombocytopenia (lasting > 10 days)
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

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 recurs, 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 bleed requiring medical intervention should be discussed with the 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.

6.5.1.2 Zanubrutinib Dose Reduction for Non-hematologic Toxicity

For non-hematological 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, follow the dose reductions described in Table 2. For subjects experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled, the study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator. Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.7.5.

6.5.2 Ibrutinib

Table 3 below describes the dose reduction levels for ibrutinib.

Table 3. Ibrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Ibrutinib (Arm B)
First	0 = starting dose	Restart at 420 mg once daily
Second	-1 dose level	Restart at 280 mg once daily
Third	-2 dose level	Restart at 140 mg once daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Ibrutinib should be interrupted for ≥ Grade 3 non-hematologic toxicities, ≥ Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib therapy may be re-initiated at the starting dose. If the toxicity recurs, reduce dose by 1 dose level (280 mg orally once daily). A second dose reduction to dose level -2 (140 mg orally once daily) may be considered as needed. If these toxicities persist or recur following 2 dose reductions, discontinue ibrutinib.

Recommended dose for ibrutinib, if co-administered with a moderate CYP3A inhibitor, posaconazole at doses ≤ 200 mg twice daily, or voriconazole at any dose, is 140 mg orally once daily.

For patients with mild hepatic impairment (Child-Pugh Class A), recommended dose for ibrutinib is 140 mg orally once daily.

6.6 Discontinuation from Study Treatment

Patients should discontinue study treatment for the following:

- Withdrawal from the study (see Section 5.13).
- Pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Intercurrent illness that compromises the patient's ability to participate in the study
- Unequivocal disease progression
    - Patients should remain on study treatment until disease progression is confirmed by independent central review.
    - Note that patients with disease progression may continue study drug treatment if they are benefiting from the treatment in the judgment of the investigators, with approval from the medical monitor.
- Need for prohibited medication
- Start of alternative anticancer therapy to treat the condition initially being evaluated in this study, or start of therapy for secondary malignancy that would interfere with assessment of zanubrutinib safety and efficacy
- Study drug interruption > 28 days (unless agreed by the investigator and the medical monitor)
- Significant, persistent, or recurrent AEs as described in Section 6.5

The investigator/patient may elect to discontinue study treatment for reasons other than those listed above, but are not required to do so. Withdrawal of consent to the study is not required to discontinue study treatment.

7 CONCOMITANT THERAPY

7.1 Concomitant Therapy

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

Patients with high tumor burden should be monitored closely, and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards for tumor lysis syndrome.

7.1.1 Permitted Medications

The following treatments are allowed:

- Blood product transfusion and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-CLL/SLL indications with the following restrictions:

  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). 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

Tumor lysis syndrome has not been currently reported with zanubrutinib treatment, but has been reported infrequently with ibrutinib. Patients with high tumor burden should be monitored closely, and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards.

Infection prophylaxis should be as per institutional standards.

7.1.2 Prohibited Medications

Patients should not receive other anticancer therapy (including but not restricted to chemotherapy, immunotherapy, corticosteroids for treatment of CLL, experimental therapy, radiotherapy, and herbal medications) while on treatment in this study. Other anticancer therapies should not be administered until disease progression (as per clinical practice standards at the study center), un-manageable toxicity, or no further clinical benefit occurs, which requires permanent discontinuation of the study drug.

7.2 Potential Interactions Between the Study Drugs and Concomitant Medications

7.2.1 QT-Prolonging Medications

Drugs known to prolong the QT/QTc interval should be avoided, in accordance with US FDA Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (2005). A list of drugs with QTc prolongation potential is provided in Appendix 9. If a patient requires treatment with any of these medications on study and a non-QT-prolonging alternative medication is not available, the medical monitor must be notified. Upon approval by the medical monitor, treatment with study drug (zanubrutinib or ibrutinib) should be withheld immediately and re-commence at least 5 half-lives following the last use of the QT-prolonging medication.

7.2.2 CYP-Inhibiting/Inducing Drugs

7.2.2.1 Zanubrutinib

Clinical studies to assess the drug interaction potential are ongoing. Based on available nonclinical metabolism data, zanubrutinib is primarily metabolized by CYP3A. Avoid concomitant administration of zanubrutinib with strong CYP3A inhibitors or strong CYP3A inducers. Grapefruit juice and Seville oranges should also be avoided, as they may affect the metabolism of zanubrutinib. For short-term use (treatment for ≤ 7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting zanubrutinib therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations. Refer to Appendix 5 for examples of strong CYP3A inhibitors and CYP3A inducers.

Based on in vitro data, zanubrutinib may have the potential to be a moderate inhibitor of the human isoenzymes CYP2C8, CYP2C9, and CYP2C19. Drugs that are primarily metabolized by these isoenzymes should be used with caution when administering zanubrutinib, with monitoring of drug concentrations where appropriate (refer to Appendix 10 for examples of these medications).

7.2.2.2 Ibrutinib

Co-administration of strong or moderate CYP3A4 inhibitors with ibrutinib may lead to increased ibrutinib exposure and, consequently, a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased ibrutinib exposure and, consequently, a risk for lack of efficacy. Therefore, concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors/inducers should be avoided.

If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A4 inhibitor must be used, reduce ibrutinib treatment to 140 mg for the duration of the inhibitor use.

Do not take ibrutinib with grapefruit or Seville oranges (bitter oranges) - this includes eating them, drinking the juice, or taking a supplement that might contain them. This is because it can increase the amount of ibrutinib in the blood. Reduce ibrutinib dose to 140 mg orally once daily during co-administration with posaconazole at doses ≤ 200 mg twice daily, and avoid ibrutinib with posaconazole at doses > 200 mg twice daily. Reduce ibrutinib dose to 140 mg orally once daily during co-administration with any dose of voriconazole. Refer to Appendix 5 for examples of strong and moderate CYP3A inhibitors and CYP3A inducers.

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 condition 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) related 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 make an assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03.

Toxicities that are not specified in the NCI-CTCAE will follow general NCI-CTCAE guidance as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or non-invasive 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. Assessment of AE severity should be based on the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 11).

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 transmission 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 in light of 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 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. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. 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 postmortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be re-sent to the sponsor within the time frames outlined in Section 8.6.1.

8.1.2 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation) or other abnormal assessments (ECG, radiographical studies, and 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 hematologic toxicities, refer to the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 11).

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 5.7.5

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 was 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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

- 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.

- Results in a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (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 is any adverse drug event, the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure. This refers to any AE that has not been previously observed (eg, included in the Investigator's Brochure), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

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. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug.

After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

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?

8.5 Specific Instructions for Recording Adverse Events and Serious Adverse Events

8.5.1 Disease Progression

Disease progression is expected in this study population, and the term "disease progression" should not be reported as an AE term. If a patient has Richter's transformation, the term "Richter's transformation/transformation" should not be recorded as the AE. This should be treated as disease progression. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the AE term(s). For instance, a patient with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as "pleural effusion" instead of disease progression or metastasis to lungs. If a patient has a seizure that is determined to be associated with a brain metastasis, the term "seizure" should be recorded as the AE instead of disease progression or brain metastasis. If a patient experiences multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the AE instead of 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. They should not be reported as SAE. A patient death not solely due to disease progression as assessed by the investigator should be reported as an SAE immediately, regardless of relationship to study drug.

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

8.5.2 Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death," "death of unknown cause," or "death unexplained."

8.6 Prompt Reporting of Serious Adverse Events

8.6.1 Time Frames for Submitting Serious Adverse Events

SAEs will be reported promptly (within 24 hours) to the sponsor or designee as described once the investigator determines that the AE meets the protocol definition of an SAE.

Table 4. Time Frame for Reporting SAEs to the Sponsor or Designee Completion and Transmission of the Serious Adverse Event Report

	Time frame for making initial report	Documentation method	Time frame 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 or pregnancy form

Abbreviation: SAE, serious adverse event.

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours. The SAE report will always be completed as thoroughly as possible with all available details of the SAE 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.

8.6.2 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.1 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 toward 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)/IEC.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

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.

8.7 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 study drug, 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 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 AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an 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 an SAE.

8.8 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.

8.9 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent 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 SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- [redacted]
- Ibrutinib 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. Data will be listed and summarized according to sponsor-agreed reporting standards.

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 ORR (PR or higher, defined as CR/CRi + PR + nodular PR) determined by independent central review using the "modified" 2008 IWCLL guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2) and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL (Appendix 3).

9.1.2 Secondary Endpoints

Key Secondary Endpoint:

- PFS, defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, determined by independent central review

Other Secondary Endpoints:

- PFS determined by investigator assessment
- Duration of response, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first, determined by independent central review
- Duration of response by investigator assessment
- Time to treatment failure, defined as time from randomization to discontinuation of study drug due to any reason

- Rate of PR-L or higher, defined as the proportion of patients who achieve a CR/CRi + PR + nodular PR + PR-L determined by independent central review
- Overall survival, defined as the time from randomization to the date of death due to any cause
- PROs measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs

[redacted]

9.2 Statistical Analysis

9.2.1 Randomization Methods

Patients will be randomized using the Interactive Response Technology system for this study by permuted block stratified randomization.

The stratified randomization using age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del[17p]/TP53 mutation status (present versus absent) as stratification factors will be produced, reviewed, and approved by an independent statistician.

9.2.2 Analysis Sets

The Intent-to-Treat Analysis Set includes all randomized patients. The Intent-to-Treat Analysis Set will be the primary analysis set for 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 drug and had no major protocol deviations. Criteria for exclusion from the Per-protocol Analysis Set will be determined and documented before the database lock for the primary analysis. For the primary analysis of non-inferiority testing in ORR by independent central review, the Per-protocol Analysis Set will be used as the secondary population.

[redacted]

9.2.3 Subject Disposition

The number of patients screened, randomized, treated, and discontinued from study drug (defined as those who discontinued study drug due to any reason except for PD) will be counted. The primary reason for study drug discontinuation will be summarized according to the categories recorded in the eCRF. The end-of-study status (alive, death, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized as recorded in the eCRF.

9.2.4 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized in the Intent-to-Treat Analysis Set using descriptive statistics. Continuous variables include age, weight, vital signs, and time since initial CLL/SLL diagnosis; categorical variables include sex, age group, race, disease stage, ECOG-PS, geographic region, and genetic status including del[17p], del[11q], 12q+, and IGHV mutation analysis.

9.2.5 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report for this protocol. Prior medications will be defined as medications that started before the first dose of study drug, whether continuing at or stopped at the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

9.2.6 Efficacy Analysis

9.2.6.1 Primary Efficacy Endpoint Analyses

The primary hypothesis testing for the primary endpoint of ORR by independent central review will be to demonstrate the non-inferiority of zanubrutinib to ibrutinib. The null and alternative hypotheses for the non-inferiority test are as follows:

- H_{0NI}: Response Ratio (zanubrutinib/ibrutinib) ≤ 0.8558
- H_{aNI}: Response Ratio (zanubrutinib/ibrutinib) > 0.8558

One interim analysis will occur approximately 12 months after 268 patients (67% information fraction) have been randomized. The final analysis will occur approximately 12 months after 400 patients have been randomized.

A Cochran-Mantel-Haenszel test for response ratio adjusting for the 4 randomization stratification factors (age [$<$ 65 years versus $\geq$ 65 years], geographic region (China versus non-China), refractory status [yes or no], and del[17p]/TP53 status [present versus absent]) will be performed for the hypothesis testing. The p-value from the test will be compared against the monitoring boundaries

for the non-inferiority testing (Table 5) and used for the primary inference. The treatment effect in ORR and its 95% Wald confidence interval (CI) will be estimated, and the Clopper-Pearson 95% CIs will be calculated for ORR for each treatment group.

If the non-inferiority is demonstrated either at the interim or the final analysis, further testing for the superiority of zanubrutinib to ibrutinib will be performed (Brannath et al 2003). The null and alternative hypotheses for the superiority test are as follows:

- $H_{0\ SUP}$: Response Ratio (zanubrutinib/ibrutinib) ≤ 1
- $H_{a\ SUP}$: Response Ratio (zanubrutinib/ibrutinib) > 1

The monitoring boundaries for the non-inferiority and superiority tests are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function and are listed in Table 5 and Table 6. The monitoring boundaries will be adjusted based on the actual information fraction (number of subjects for ORR) observed up to the data cutoff. Deviation from the scheduled interim analysis will not affect the overall type I error (Lan and DeMets 1983).

Table 5. Monitoring Boundaries for the ORR Non-inferiority Testing

	Number of patients evaluable	Information fraction	Nominal p-value boundary (primary inference)	Response ratio boundary
Interim	268	67%	0.006	1.062
Final	400	100%	0.023	0.985

Abbreviation: ORR, overall response rate.

Table 6. Monitoring Boundaries for the ORR Superiority Testing

	Number of patients evaluable	Information fraction	Nominal p-value boundary (primary inference)	Response ratio boundary
Interim	268	67%	0.006	1.241
Final	400	100%	0.023	1.151

Abbreviation: ORR, overall response rate.

Justification of the Non-inferiority Margin

A non-inferiority margin of 0.8558 in response ratio was derived using the 95% to 95% fixed margin approach (FDA Guidance for Industry Non-Inferiority 2016). In the RESONATE trial (Byrd et al 2014), the ibrutinib effect over ofatumumab represented by the ratio of response rate (PR or higher) was 10.43 with a 95% CI of (5.2, 21.0) based on the independent review committee assessment. In the RESONATE2 trial (Burger et al 2015), the ibrutinib effect over chlorambucil represented by the ratio of response rate (PR or higher) was 2.33 with a 95% CI of (1.83, 2.97)

based on the independent review committee assessment. In a fixed-effect meta-analysis of the 2 studies using inverse variance weighting, the ibrutinib effect in response rate ratio is estimated as 2.7392 with a 95% CI of (2.1781, 3.4450). Thus, M1 is 2.1781, the lower bound of the 95% CI. Since the effect sizes of ibrutinib are over active controls in both studies (ofatumumab and chlorambucil, respectively), rather than placebos, the choice of M1 is very conservative and results in a narrow margin. Requiring 80% of M1 to be retained (on the log scale) in zanubrutinib to demonstrate non-inferiority generates a non-inferiority margin of 0.8558 (for the response ratio), which is within the clinically acceptable limit.

9.2.6.2 Secondary Efficacy Endpoint Analyses

If the primary objective of demonstrating the non-inferiority of zanubrutinib to ibrutinib in ORR by independent central review is met, the treatment effect of the key secondary efficacy endpoint of PFS by independent central review will be tested for non-inferiority under hierarchical testing to control the study-wise type I error.

If non-inferiority is demonstrated for the key secondary efficacy endpoint of PFS by independent central review, further testing of superiority will be performed for the endpoint (Brannath et al 2013).

Treatment arm comparison for the other secondary efficacy endpoints will be descriptive, and no hypothesis testing will be performed.

Key Secondary Efficacy Endpoints

Progression-free Survival by Independent Central Review

The non-inferiority of zanubrutinib to ibrutinib for PFS determined by independent central review will be tested under the non-inferiority margin of 1.3319 (for the hazard ration [HR] of zanubrutinib/ibrutinib) using a stratified log-rank test based on the 4 randomization stratification factors: age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del[17p]/TP53 mutation status (present versus absent). The null and alternative hypotheses to test the non-inferiority are as below:

- H_{0NI}: HR (zanubrutinib/ibrutinib) ≥ 1.3319
- H_{aNI}: HR (zanubrutinib/ibrutinib) < 1.3319

There will be 2 analyses to test the non-inferiority of PFS by independent central review: an interim analysis at the time of the ORR final analysis and a final analysis when 205 events have occurred. Ninety-three (93) PFS events are expected to accrue at the time of the ORR final analysis. Two hundred five (205) PFS events are expected to accrue [redacted] months after study start (as described in Section 9.4). If the p-value from the stratified log-rank test meets the non-inferiority monitoring boundary at either the interim or the final analysis, the non-inferiority of zanubrutinib to ibrutinib in terms of PFS by independent central review will be demonstrated. Further testing of superiority in terms of PFS by independent central review will be performed in this case. Table 7 and Table 8 include the monitoring boundaries of the PFS non-inferiority and superiority tests at the interim (assuming 93 PFS events) and the final analysis. The monitoring boundaries are based on O'Brien-

Fleming boundary approximated by the Lan-DeMets spending function. The monitoring boundaries will be adjusted based on the actual information fraction (number of events for PFS) observed up to the data cutoff. Deviation from the scheduled interim analysis will not affect the overall type I error (Lan and DeMets 1983).

Table 7. Monitoring Boundaries for the PFS Non-Inferiority Testing

	Time (months)	# PFS events	Nominal p-value boundary (primary)	HR boundary
Interim analysis	[redacted]	93	0.0009	0.6960
Final analysis	[redacted]	205	0.0247	1.0122

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

Table 8. Monitoring Boundaries for the PFS Superiority Testing

	Time (months)	# PFS events	Nominal p-value boundary (primary)	HR boundary
Interim analysis	[redacted]	93	0.0009	0.5235
Final analysis	[redacted]	205	0.0247	0.7594

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

The non-inferiority margin of 1.3319 was derived using the 95%-95% fixed margin method based on a meta-analysis of the RESONATE and RESONATE 2 studies. In the RESONATE2 study, the estimated PFS HR for ibrutinib versus chlorambucil is 0.16 with a 95% CI of (0.09, 0.28). In the updated RESONATE results (Brown et al 2014), the estimated PFS HR for ibrutinib versus ofatumumab is 0.106 with a 95% CI of (0.073, 0.153). In a fixed-effect meta-analysis, the pooled HR is estimated as 0.120 with a 95% CI of (0.088, 0.163). Therefore, the control arm effect (M1) is -0.163 in HR and 1.814 in log HR. Requiring 84.2% of M1 to be retained in zanubritinib, a non-inferiority margin of 1.3319 for the HR (zanubrutinib/ibrutinib) is generated.

The HR for PFS by independent central review and its 95% CI will be estimated from a stratified Cox regression model.

The distribution of PFS including median and other quartiles, and PFS rate at selected timepoints, will be estimated using the Kaplan-Meier method for each arm.

PFS will be calculated as the time from the date of the randomization to the date of the first documentation of disease progression or death due to any cause, regardless of the use of subsequent anticancer therapy prior to the documented PD or death. PFS for the patients without a documented PD or death will be censored at the last disease assessment.

Other Secondary Efficacy Endpoints

PFS Determined by Investigator Assessment

The HR for PFS by investigator assessment and its 95% CI will be estimated from a stratified Cox regression using the four randomization stratification factors (age [< 65 years versus ≥ 65 years],

geographic region (China vs non-China), refractory status [yes or no], and del[17p]/TP53 status [present versus absent]). Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group.

PFS will be calculated as the time from the date of randomization to the date of first documentation of disease progression (as assessed by investigator assessment) or death due to any cause, regardless of the use of subsequent anti-cancer therapy prior to documented PD or death. PFS for the patients without a documented PD or death will be censored at the last disease assessment.

Duration of Response

The distribution of DOR by independent central review including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group. There will be no treatment arm comparison for DOR. The same analysis will be performed for DOR by investigator assessment. The same censoring rule used in the PFS analysis will be used for the analysis of DOR.

Time to Treatment Failure

The HR for time to treatment failure and its 95% CI will be estimated from a stratified Cox regression using the 4 randomization stratification factors (age [< 65 years versus ≥ 65 years], geographic region (China versus non-China), refractory status [yes or no], and del[17p]/TP53 status [present versus absent]). The Kaplan-Meier method will be used to estimate the distribution of time to treatment failure for each treatment group.

Time to treatment failure will be calculated as the time from the date of randomization to the date of discontinuation of study treatment due to any cause. Time to treatment failure will be censored at the data cutoff for the patients who did not discontinue study treatment.

Rate of PR-L or Higher by Independent Central Review

Rate of response ratio for PR-L or higher by independent central review and its 95% Wald CI will be estimated using the Cochran-Mantel-Haenszel method. Clopper-Pearson 95% CI for the rate of response will be calculated for each treatment group.

Overall Survival

OS will be analyzed using the same methods employed for PFS by investigator assessment.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint for each treatment group. 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 2 treatment groups. The data may also be analyzed using repeated measure mixed model to account for missing data under the Missing at Random assumption.

Changes in the EQ-5D-5L will be summarized for each treatment group.

[redacted]

9.2.6.4 Sensitivity Analyses

Overall response rate by investigator assessment will be analyzed as a sensitivity analysis. The analysis methods in the primary endpoint analysis will be repeated in this analysis.

A multiple logistic regression analysis for ORR by independent central review will be performed to explore the relationship between the baseline prognostic factors and ORR by independent central review and to estimate the treatment effect adjusted for the imbalances in these factors.

For PFS, alternative censoring rules such as censoring for new anticancer therapy will be used as sensitivity analyses. A multiple Cox regression analysis will be performed to explore the relationship between the baseline prognostic factors and PFS by independent central review, and to estimate the treatment effect adjusted for the imbalances in these factors.

Subgroup analyses for ORR by independent central review and selected secondary endpoints will be performed.

[redacted]

9.3 Safety Analyses

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v4.03. Laboratory values (CBC, serum chemistry, and coagulation), vital signs, physical exams, and ECG findings will also be used in the safety assessment. Descriptive statistics will be used to analyze all safety data by the actual treatment group.

9.3.1 Extent of Exposure

The extent of exposure to the 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 category.

Patient data listings will be provided for all dosing records.

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) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class will also be captured in the database.

A treatment-emergent AE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days following the study drug discontinuation or the start of a new anticancer therapy, whichever comes first. After this period, only treatment-related SAEs are to be reported (per Section 8.4.1). Only the AEs that are treatment emergent will be included in the summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of treatment-emergent AEs will be reported as the number (and percentage) of patients with treatment-emergent 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 treatment-emergent AEs within a specific system organ class and preferred term. The number (percentage) of patients with treatment-emergent AEs will also be summarized by the relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to the study drug or with a missing assessment of the causal relationship. SAEs, deaths, treatment-emergent AEs ≥ Grade 3, study drug-related treatment-emergent 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

Selected CBC components 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 of (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for the laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by the 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, phosphorus, potassium, sodium) will be summarized separately.

9.3.4 Vital Signs

Descriptive statistics for the vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, and weight) and the 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 as described in Section 5.4.4 and in Appendix 12. Descriptive statistics for absolute and change from baseline ECG parameters will be presented.

9.4 Sample Size Consideration

The sample size calculation is based on the primary efficacy analysis for the primary endpoint of ORR by independent central review. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.25 (75%/60%), 400 patients will provide more than 99% power to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio) and 1-sided alpha level of 0.025 when there is 1 interim analysis at 67% information fraction. Four hundred (400) patients will provide 88% power to demonstrate superiority at the 1-sided alpha level of 0.025 under the alternative hypothesis (response ratio = 1.25, 75% versus 60%) with 1 interim analysis. The power for superiority will be 70.3% under the alternative hypothesis of a response ratio of 1.2 (72% versus 60%).

Assuming an HR (zanubrutinib arm/ibrutinib arm) of 0.9, 205 events are required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the non-inferiority of zanubritinib to ibrutinib at the non-inferiority margin of 1.3319 (HR) in PFS by independent central review, when 1 interim analysis is expected at 45% (expected number of events at the final ORR analysis) of the target number of events.

If the 400 patients are randomized in a 1:1 ratio to the 2 arms over a 17-month period including a 9-month ramp-up period before reaching the peak enrollment of 33 patients/month with a 0.0017/month hazard rate for drop-out, 205 events are expected to be accumulated in [redacted] months from study start. A median PFS of [redacted] months for ibrutinib and an exponential distribution for PFS are also assumed.

9.5 Interim Analysis

There will be 1 interim analysis for the non-inferiority (and the superiority if the non-inferiority is met) testing of ORR by independent central review. The interim analysis will be performed approximately 12 months after the randomization of 268 patients. The monitoring boundaries for the interim and the final analyses for the non-inferiority and superiority tests are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function and are depicted in Table 5 and Table 6 (Section 9.2.6.1).

If the boundary is met for the interim non-inferiority analysis and the DMC recommends stopping the study, the sponsor may stop the study and file the results to the regulatory agencies for approval.

There will be 1 interim analysis for the non-inferiority testing of the key secondary efficacy endpoint of PFS by independent central review. The interim analysis for PFS will occur at the time of the ORR final analysis, which is expected to occur at [redacted] months after study start. Ninety-three (93) PFS events are expected to occur by the interim analysis. The O'Brien-Fleming boundary approximated by the Lan-DeMets spending function will be implemented and the nominal p-value boundaries will be used for the primary inference in the interim and the final analyses (presented in Table 7 and Table 8 in Section 9.2.6.2).

9.6 Final Analysis

If the primary objective of the ORR non-inferiority is met, the study will continue to follow up for PFS until 205 events are observed, which is estimated to be approximately [redacted] months from study start. The stopping boundaries for the PFS final analyses are shown in Table 7 and Table 8 in Section 9.2.6.2.

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 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 and also perform the interim efficacy analysis. 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 this study. This will be conducted by qualified, board-certified radiologists and hematologists assigned to this study. 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 Clinical Study Report 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 of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results would 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 an 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 Council on Harmonisation guidelines and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations 312, Subpart D, "Responsibilities of sponsors and Investigators," 21 Code of Federal Regulations, Part 50, and 21 Code of Federal Regulations, Part 56, are adhered to.

11.2.2 Ethical Conduct of the Study and Ethics Approval

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

The sponsor's sample ICF will be provided to each investigator who shall adapt it, subject to sponsor's approval, for use at his/her site. The investigator (or sponsor, where applicable) is responsible for ensuring that: 1) this protocol, 2) the study center's ICF, and 3) any other information or forms that will be presented to potential patients (eg, advertisements, Health Insurance Portability and Accountability Act of 1996 authorization, 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 ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

11.2.2.1 Protocol Amendments

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted by the investigator (or sponsor, where applicable) 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 - 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.

If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator (or sponsor, where applicable) 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 ICF 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 ICF/other information and the approved amended ICF/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 ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent must 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.

In the event that the ICF or other form signed by the patient is amended during their participation in the study, patients must be re-consented to the most current version of the ICFs or form. For any updated or revised ICFs or forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was reobtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site master study file and must be available for verification by study monitors at any time.

11.2.4 Investigator Reporting Requirements

As indicated in Section 8.6.2, 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

The investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

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 ICF process, either as part of the ICF or as a separate signed document (for example, in the United States, a site-specific Health Insurance Portability and Accountability Act of 1996 consent may be used).

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location. Only patient initials (where allowed), date of independent central review, and an identification code (ie, not names) should 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 Investigator's Brochure, this protocol, eCRFs, 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.

If the written contract for the conduct of the study includes confidentiality provisions regarding BeiGene's confidential information inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

11.2.6 Data Collection

Data required by the protocol will be entered into an EDC system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Statement of Investigator Form must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

11.2.7 Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the course of the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

AEs will be coded using the MedDRA Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.0 or higher.

11.2.8 Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or sharing such outputs from the EDC system with other

functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the trial is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

11.2.9 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, quantities dispensed to patients, and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, sites should have an appropriate standard operating procedure for study drug disposal/destruction. 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 and applicable law, including that regarding disposal of hazardous waste. 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.

11.2.10 Inspections, Audits, and Monitoring Visits

The investigator must ensure the facilities used for this trial and all the 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.

11.2.11 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.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and, if applicable, to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

11.2.12 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 interest of clinical investigators and/or disclose those financial

interests, as required by 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 Study Report and Publications

A Clinical Study Report 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 trial are the exclusive property of the sponsor and are confidential. For multicenter studies, 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).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met***:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for the earlier of: at least 2 years or the period indicated in the clinical study agreement.

No such communication, presentation, or publication will include BeiGene's confidential information.

[redacted]

[redacted]

11.4 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
- [redacted]

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 with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. 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 still be provided 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.

11.5 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, eCRF 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 eCRFs) 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 or responsibility for 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.

[redacted]

11.6 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) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights, whether or not patentable, 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 in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 11.3.

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.

11.7 Joint Investigator/Sponsor Responsibilities

11.7.1 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 in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs 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 eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected or queries raised in the course of these monitoring visits are resolved.

11.7.2 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 cooperate with representatives of a regulatory agency and BeiGene and to provide them access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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Zydelig® - Summary of Product Characteristics: 15 December 2016.

APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

PROTOCOL NO: BGB-3111-305

This protocol is a confidential communication of BeiGene, Ltd. and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. 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. or one of its subsidiaries.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene or its designee.

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[c]	Partial Response[e]	Partial Response with Lymphocytosis[g]	Progressive Disease[h]
Group A				
Lymphadenopathy[a]	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	
Marrow[b]	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi[d]	50% reduction in marrow infiltrate, or B-lymphoid nodules[f]	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils[b]	> 1500/µL	> 1,500/µL or > 50% improvement over baseline	> 1,500/µL or > 50% improvement over baseline	

Abbreviations: CLL, chronic lymphocytic leukemia; CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PR, partial response.

Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

a. Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination).
b. These parameters are irrelevant for some response categories.
c. Complete response: all the criteria have to be met, and patients have to lack disease-related constitutional symptoms.
d. Complete response with incomplete marrow recovery: all the criteria met for complete response except for hypocellular bone marrow.

e. Partial response: at least 2 of the criteria of group A plus 1 of the criteria of Group B must be met.
f. Nodular partial response: all the criteria met for complete response except for the presence of lymphoid nodules in the bone marrow
g. Partial response with lymphocytosis: blood lymphocytes decreased < 50% or increased from baseline + 1 Group A parameter met OR 2 Group A parameters met + lymphocytosis
h. Progressive disease: at least 1 of the above progressive disease criteria must be met.

- Stable disease: is absence of progressive disease and failure to achieve at least a PR
- Indeterminate response due to zanubrutinib hold: see below.

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. 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 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. THE LUGANO CLASSIFICATION FOR CT-BASED RESPONSE FOR SLL (CHESON ET AL 2014)

Response and Site	CT-Based Response
Complete	
Lymph nodes and extralymphatic sites	Complete radiologic response (all of the following): • 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, IHC negative
Partial	
Lymph nodes and extralymphatic sites	Partial remission (all of the following): • ≥ 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	
Target nodes/nodal masses, extra-nodal lesions	Stable disease < 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

Response and Site	CT-Based Response
Bone marrow	Not applicable
Progressive disease*	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
Individual target nodes/nodal masses	
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

Source: Cheson et al 2014.
Abbreviations: CT, computed tomography; IHC, immunohistochemistry.

Modification from Lugano Classification for NHL (Cheson et al, 2014**):**

*Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days 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 during periods of zanubrutinib hold will not be considered as progressive disease unless confirmed by 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.

**Splenomegaly defined as vertical spleen length > 13 cm.

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

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
CYP3A4, CYP3A5, CYP3A7
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)
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam, cimetidine
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Source: Food and Drug Administration Center for Drug Evaluation Research (CDER) 2012.

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.

Note: 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.

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	☐

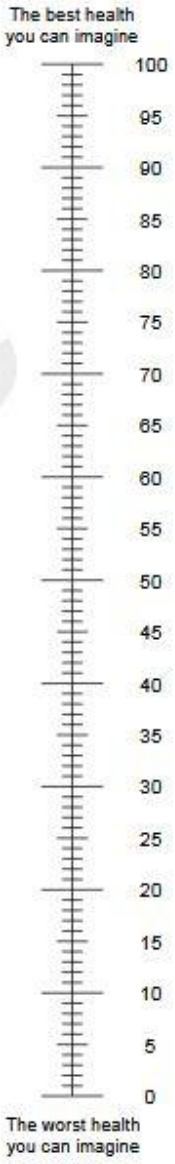
ANXIETY / DEPRESSION

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 = ☐



3

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. MEDICATIONS WHICH ARE KNOWN TO POLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES

Antiarrhythmics	amiodarone disopyramide dofetilide flecainide ibutilide procainamide quinidine sotalol
Anticancer	arsenic trioxide vandetanib
Antihistamines	astemizole terfenadine
Antibiotics	azithromycin clarithromycin erythromycin moxifloxacin sparfloxacin
Anti-anginal	bepridil
Anti-malarial	chloroquine halofantrine
Anti-psychotics	chlorpromazine haloperidol mesoridazine pimozide thioridazine
Anti-nausea	domperidone droperidol dolasetron (intravenous and oral)
Anti-infective	pentamidine
Anti-lipemic	probucol
Antidepressants	citalopram
Opiate agonists	levomethadyl methadone
GI stimulant	cisapride

Source: Arizona Center for Education and Research on Therapeutics (CERT) 2017.

Note: The list of medications presented above is not necessarily comprehensive and Investigators should refer to prescribing information of concomitant medications for any relevant QT prolongation potential.

APPENDIX 10. SENSITIVE CYP2C8, CYP2C9, AND CYP2C19 SUBSTRATES OR CYP2C8, CYP2C9, AND CYP2C19 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX

CYP2C8 Substrates	CYP2C9 Substrates	CYPC19 Substrates
repaglinide[1]	celecoxib	**Anti-epileptics:**
paclitaxel	phenytoin[2]	S-mephenytoin[1,2]
	warfarin[2]	
		Proton Pump Inhibitors
		lansoprazole[1]
		omeprazole[1]

Abbreviations: AUC, area under the plasma concentration time curve; CYP, cytochrome P450; NTI, narrow therapeutic index.

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg Torsades de Pointes).

Source: Food and Drug Administration Center for Drug Evaluation Research (CDER) 2012.

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for drug interaction information or contact the medical monitor of the protocol.

APPENDIX 11. 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%	≥ 2,000
1	11%-24%	≥ 1,500 and < 2,000
2	25%-49%	≥ 1,000 and < 1,500
3	50%-74%	≥ 500 and < 1,000
4	≥ 75%	< 500

Source: Hallek et al 2008.

Abbreviation: ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia
Hgb: hemoglobin; WBC, white blood cell;

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 (1,000/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 (1,000/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 12. SCHEDULE OF ASSESSMENTS

	Screening	Treatment (1 cycle = 28 days)					Continue Assessments Until Disease Progression	Post-Treatment Follow-Up	
Cycle	**–**	**1**	**2 to 3**	**4**	**5 to 6**	**Cycles 7, 10, 13, 16, 19, 22, 25, then every 6 cycles**		**Safety Follow-up[a]**	**Long-term Follow-up[b]**
Cycle Day	**-35 to -1**	**1**	**1**	**1**	**1**	**1**		**30 days after EOT**	**Every 6 months**
Window (Days)	**–**	**-**	**± 4**	**± 4**	**± 4**	**± 7**		**+ 7 days**	**± 14 days**
Informed consent, screen number[c]	X								
Medical & cancer history	X								
Eligibility authorization packet[d]	X								
Randomization/Treatment arm assignment[e]	X								
Zanubrutinib & ibrutinib dispensing/accountability[f]		X	X	X	X	X			
[redacted]	[redacted]								
Safety Assessments									
Cardiac function	X								
Vital signs (temperature, BP, heart rate)	X	X	X	X	X	X		X	
Physical examination[h]	X	X	X	X	X	X		X	
ECOG performance status	X	X	X	X	X	X		X	
12-Lead ECG (local read)[i]	X	X	X	X		X			
Concomitant medications review	X	X	X	X	X	X		X	X
AE review[j]		X	X	X	X	X		X	X
Efficacy Assessments									
Overall response assessment				X		X		X	X
Disease-related constitutional symptoms	X			X		X		X	X
Exam of liver, spleen & lymph nodes	X			X		X		X	X
CT with contrast[k]	X			X		X		X[l]	X
Bone marrow examination[m]	X	As needed[m]							
PRO questionnaires[n]		X		X		X		X	X
Laboratory Assessments									
Hematology[o], chemistry[p,q]	X	X	X	X	X	Every cycle		X	X
Serum immunoglobulins	X			X		C7 then every 6 cycles			
Coagulation[s]	X								
del[17p], cytogenetics[t]	X								
IGHV mutation [redacted]	X					X[u]		X[u]	
Hepatitis B & C testing[v]	X								
Pregnancy test (if applicable)[w]	X	X	X	X	X	Every cycle			

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; BTK, Bruton tyrosine kinase; C#, Cycle #; CR, complete response; CRi, complete response with incomplete bone marrow recovery; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IEC, Independent Ethics Committee; IGHV, immunoglobulin variable region heavy chain; INR, international normalized ratio; MRI, magnetic resonance imaging; [redacted] PD, progressive disease; [redacted] s; PRO, patient-reported outcome; SAE, serious adverse event.

a. Approximately 30 days (± 7 days) after permanent treatment discontinuation or before initiation of a new anticancer therapy, whichever comes first.
b. Visits repeat every 6 months (± 14 days) after Safety Follow-up. Assessments include survival status and subsequent therapies for CLL/SLL, and may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic disease progression.
c. Informed consent and assignment of screen number 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 IEC.
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 and the medical monitor or designee will provide final approval for 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 randomized 1:1 to 1 of 2 arms - Arm A: zanubrutinib or Arm B: ibrutinib. Study treatment must commence within 5 days after randomization/treatment assignment.
f. Zanubrutinib will be administered 160 mg orally twice daily with or without food. Ibrutinib will be administered 420 mg orally once daily.
g. [redacted]
h. Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at Screening only). Assessment of vital signs and a focused physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days.
i. Perform a 12-lead ECG in triplicate at screening for all subjects. For subjects assigned to the zanubrutinib arm, one 12-lead ECG will be performed at, pre-dose (within 30 min prior to dose) and 2 hours (± 30 min) post-dose on Day 1 of Cycles 1 and 2, and one 12-lead ECG performed on Day 1 of Cycles 3 and 4 and Day 1 of every 3 cycles thereafter (at Cycle 7, Cycle 10, etc) until EOT. The ECG can be performed at either pre-dose or post-dose. For subjects assigned to the ibrutinib arm, a 12-lead ECG in triplicate will be performed at Day 1 of Cycles 1, 2, 3, and 4 and Day 1 of every 3 cycles thereafter (Cycle 7, Cycle 10, etc) until EOT. The ECG can be performed at either pre-dose or post-dose.
j. Collect non-serious AE information from the time of first dose of study drug through Safety Follow-up. Collect SAE information from the time of signed informed consent through screen failure or Safety Follow-up. In addition, arrhythmia signs/symptoms will be reviewed at every cycle. This will involve the investigators asking subjects for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness or fainting), as part of the routine AE monitoring for each cycle.
k. CT with contrast of neck, chest, abdomen, and pelvis to be performed at Screening, Cycle 4 Day 1, then every 3 cycles for 25 cycles, followed by every 6 cycles (± 7 days) thereafter, until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Copies of all scans will be sent for independent central review for response assessment. MRI may be substituted for patients with serious contrast allergy, but should be used consistently. In Germany, a MRI may be used in place of CT in all patients.
l. A CT scan does not need to be repeated if performed within 45 days before the Safety Follow-up Visit.
m. Bone marrow biopsy and aspirate are required during the screening period to perform pathology and flow cytometry. Bone marrow biopsy and aspirate are

required under the following conditions during the treatment period: if clinical and laboratory results demonstrate a potential CR or CRi, to confirm a CR or CRi ([redacted]); progression of cytopenias unrelated to autoimmune cytopenias or study treatment, in order to confirm PD. Patients who are otherwise complete responders, but show bone marrow involvement, should recheck bone marrow as clinically indicated, but at a minimum at least once per year until CR or CRi is confirmed. All bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory.

n. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug, and before performing any other procedures. The questionnaires are to be completed on Cycle 1 Day 1, Cycle 4 Day 1, then every 3 cycles for 25 cycles, followed by every 6 cycles thereafter until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.

o. Complete blood count and differential will be evaluated by a central laboratory, and is required on Cycle 1 Day 1, then on Day 1 (± 4 days) of each cycle, and during Safety Follow-up and Long-term Follow-up. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil).

p. Serum chemistry is required on Cycle 1 Day 1, then on Day 1 (± 4 days) of each cycle and will be evaluated by a central laboratory. Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase.

q. The following 2 chemistry tests will only be done at Screening and performed locally: direct antiglobulin test and β-2 microglobulin.

r. In Cycle 1, laboratory assessments should be done before the first study drug administration.

s. Prothrombin time, INR, and aPTT will be evaluated by a central laboratory.

t. Blood samples are required at the time of Screening and shipped to the testing laboratory (see the Laboratory Manual for details)

u. Blood samples will be collected at Screening, at the time of CR or CRi, [redacted] and shipped to the testing laboratory (see the Laboratory Manual for details).

v. Hepatitis B serology includes HBsAg, HBcAb, HBsAb. Patients who are HBcAb positive, HBsAg negative, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly. Hepatitis C serology includes HCV antibody. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly. All hepatitis B and hepatitis C testing will be performed by local laboratories.

w. 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. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Day 1 of every cycle and for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Identifier:	BGB-3111-305
Phase:	3
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Sponsor:	BeiGene USA, Inc.
	[redacted]
Reference Number:	EudraCT 2018-001366-42
Original Protocol:	09 July 2018
Protocol Amendment 1.0:	04 August 2018
Protocol Amendment 1.1 (Spain)	07 December 2018
Protocol Amendment 1.2 (Czech Republic)	06 February 2019
Protocol Amendment 1.3 (Germany)	31 May 2019
Protocol Amendment 2.0:	29 August 2019
Protocol Amendment 3.0	31 January 2020

[redacted]

FINAL PROTOCOL APPROVAL SHEET

A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BeiGene USA, Inc. Approval:

SYNOPSIS

Name of Sponsor/Company: BeiGene USA, Inc.
Investigational Product: zanubrutinib (BGB-3111)
Title of Study: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Protocol Identifier: BGB-3111-305
Phase of Development: 3
Number of Patients: Approximately 600
Study Centers: Approximately 150

Study Objectives:

Primary

- To compare the efficacy of zanubrutinib (also known as BGB-3111) versus ibrutinib as measured by overall response rate determined by investigator assessment

Secondary

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
    - Progression-free survival determined by investigator assessment and independent central review
    - Overall response rate determined by independent central review
    - Duration of response determined by independent central review
    - Duration of response determined by investigator assessment
    - Time to treatment failure
    - Rate of partial response with lymphocytosis or higher determined by independent central review
    - Overall survival
    - Patient-reported outcomes
- To compare the safety of zanubrutinib versus ibrutinib

[redacted]

Study Design:

This is a Phase 3, randomized study of zanubrutinib versus ibrutinib in approximately 600 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The primary efficacy endpoint is overall response rate (ORR) determined by investigator assessment. While the primary efficacy endpoint is per investigator assessment, ORR per independent central review will also be analyzed to support the primary analysis. In the United States, ORR assessed by independent central review will be the basis for regulatory decisions. Disease response will be assessed per the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2008), with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2), and per Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) for patients with SLL (Appendix 3). Rate of response for partial response with lymphocytosis (PR-L) or higher will be assessed as a secondary efficacy endpoint.

The study is broken into three periods for every patient:

- Screening Period (Section 5.2)
- Treatment Period (Section 5.11)
- Post-Treatment Period
  - End of Treatment Visit (Section 5.12.1)
  - Long-Term Follow-up (Section 5.12.2)
  - Survival Follow-up (Section 5.12.3)

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent).

Treatment with zanubrutinib and ibrutinib will be open label. Study treatment will continue until disease progression, or any of the events outlined in Section 6.7. The study duration is estimated to be approximately [redacted] months (see Section 3.5).

Study Assessments

Assessments to be performed during the study include [redacted] disease-related constitutional symptoms; physical examination of liver, spleen, and lymph nodes; computed tomography (CT) scan of neck, chest, abdomen, and pelvis with contrast; bone marrow examination at screening, for patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CRi [redacted] patient-reported outcomes (PRO; European quality of life 5-dimensions 5-levels health questionnaire [EQ-5D-5L], European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire [EORTC QLQ- C30], [redacted] laboratory studies; bone marrow examination; genetic alterations in the tumor cells (eg, del 17p, del11q, 12q+ and immunoglobulin variable region heavy chain (IGHV) mutation analysis).

Patients should remain on study treatment until disease progression is confirmed by independent central review (as described in Section 6.7).

Assessments of safety will include adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, electrocardiograms, and vital signs (Section 5.5). Adverse

events will be graded for severity per the current version of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and the Grading Scale for Hematologic Toxicities in CLL Studies (see Section 8.1.1.1). An independent Data Monitoring Committee will periodically monitor safety data and also perform the interim efficacy analysis.

Efficacy (Section 5.6) will be assessed locally by the investigator as well as by independent central review (Section 10.3). Progression must be confirmed by independent central review (Section 6.7).

Key Eligibility Criteria:

The patients to be included in this trial will have a confirmed diagnosis of CLL or SLL that meets the International Workshop on Chronic Lymphocytic Leukemia criteria and requiring treatment as defined by at least 1 of the following: progressive marrow failure; massive, progressive, or symptomatic splenomegaly; massive, progressive, or symptomatic lymphadenopathy; progressive lymphocytosis with rapid doubling time; or constitutional symptoms. Patients must be 18 years or older, relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL, with the last dose of prior therapy for CLL/SLL > 14 days before randomization, and have measurable disease (defined as ≥ 1 lymph node > 1.5 cm in longest diameter, and measurable in 2 perpendicular diameters or an extranodal lesion must measure > 10 mm in longest perpendicular diameter). Note: A line of therapy is defined as completing at least 2 cycles of treatment of standard regimen according to current guidelines, or of an investigational regimen on a clinical trial. Patients will have no history of prolymphocytic leukemia or Richter's transformation, no currently active clinically significant cardiovascular disease, and no HIV infection or active infection with hepatitis B or C.

Test Product, Dose, and Mode of Administration:

Zanubrutinib (160 mg twice daily) will be administered orally.

Reference Therapy, Dose, and Mode of Administration:

Ibrutinib (420 mg once daily) will be administered orally.

Statistical Methods:

Efficacy Analyses

The primary analysis set for all efficacy analyses is the Intent-to-Treat Analysis Set (all patients randomized). For the non-inferiority testing for the primary endpoint of ORR, the analysis will also be performed using the Per-protocol Analysis Set.

Primary Efficacy Endpoint Analysis:

The primary efficacy analysis of ORR (PR or higher, defined as CR/CR with incomplete bone marrow recovery + PR + nodular PR) will be conducted as assessed by the investigator, using the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2008), with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2) and per Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) for patients with SLL (Appendix 3). While the primary efficacy endpoint is per investigator assessment, ORR per independent central review will also be analyzed to support the primary analysis. In the United States, ORR assessed by independent central review will be the basis for regulatory decisions.

The primary hypothesis testing for ORR is for non-inferiority. The non-inferiority of zanubrutinib to ibrutinib will be tested for the Intent-to-Treat Analysis Set under the pre-specified margin of 0.8558 (response ratio of zanubrutinib to ibrutinib). The primary objective of the study is met if the non-inferiority is demonstrated. The null and alternative hypotheses for testing ORR non-inferiority are as follows:

- H_{0NI}: Response Ratio (zanubrutinib/ibrutinib) ≤ 0.8558
- H_{aNI}: Response Ratio (zanubrutinib/ibrutinib) > 0.8558

There will be 1 interim analysis approximately 12 months after 415 patients (69% information fraction) have been randomized. The final analysis will occur approximately 12 months after 600 patients have been randomized. Based on the assumption to randomize 600 patients in ■ months, the final analysis is expected to occur ■ months after the study start.

A Cochran-Mantel-Haenszel test for response ratio adjusting for the 4 randomization stratification factors will be performed for hypothesis testing. The Cochran-Mantel-Haenszel response ratio will be estimated along with its 95% Wald confidence interval (CI). Clopper-Pearson 95% CI will be calculated for ORR for each treatment group.

If non-inferiority is demonstrated at either interim or final analysis, superiority of zanubrutinib to ibrutinib will be tested next (Brannath et al 2003). The monitoring boundaries for the non-inferiority and superiority tests are based on O'Brien Fleming type alpha spending function and depicted in Table 8 and Table 9.

Justification of Non-inferiority Margin

The non-inferiority margin was derived using the 95%-95% fixed margin method (FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness 2016). The efficacy of ibrutinib (M1) in response ratio scale was estimated as 2.1781 from the results of RESONATE and RESONATE2 trials by a fixed-effect meta-analysis. Requiring 80% of M1 to be retained in zanubrutinib, a non-inferiority margin of 0.8558 is generated. The margin is within the clinically acceptable limit.

Secondary Efficacy Endpoint Analyses

Key secondary efficacy endpoint

If the primary objective of demonstrating non-inferiority of zanubrutinib to ibrutinib in ORR is met, the key secondary efficacy endpoint of progression-free survival (PFS) by investigator assessment will be tested for non-inferiority under hierarchical testing to control study-wide type I error. There will be a single analysis of PFS when approximately 205 PFS events have occurred, and PFS will be summarized descriptively at the time ORR is significant. While the key secondary efficacy endpoint is per investigator assessment, PFS per independent central review will also be analyzed to support the key secondary endpoint analysis. In the United States, PFS assessed by independent central review will be used to support regulatory decisions.

PFS will be compared between the 2 arms using a stratified log-rank test based on the 4 randomization stratification factors. The non-inferiority margin for the test is 1.3319 in hazard ratio (HR; zanubrutinib/ibrutinib). If the p-value from the stratified log-rank test for non-inferiority is significant, the non-inferiority of zanubrutinib to ibrutinib in PFS is demonstrated, and further testing of superiority will be performed. The HR (zanubrutinib/ibrutinib) and its 95% CI will be estimated from a stratified Cox regression model. The distribution of PFS, including median and other quartiles, and PFS rate at selected timepoints will be estimated using the Kaplan-Meier method for each arm.

Other secondary efficacy endpoints:

No hypothesis testing will be performed for other secondary efficacy endpoints.

- The distribution of duration of response (DOR) by independent central review including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group. The same analysis will be performed for DOR by investigator assessment.
- The HR for time to treatment failure and its 95% CI will be estimated from a stratified Cox regression using the 4 randomization stratification factors. Kaplan-Meier method will be used to

estimate the distribution of time to treatment failure for each treatment group.

- Rate of response for partial response with lymphocytosis or higher by independent central review will be analyzed using the Cochran-Mantel-Haenszel response ratio along with its 95% Wald CI. Clopper-Pearson 95% CI for the estimate will be calculated for each treatment group.
- Overall survival will be analyzed using the same methods employed for PFS by investigator assessment.
- Patient-reported outcomes: The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint for each treatment group. Change of EQ-5D-5L score will be summarized for each treatment group.

Safety Analyses

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

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

All treatment-emergent AEs will be summarized. Serious adverse events, 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.

Sample Size Considerations

The sample size calculation is based on the primary efficacy analyses for the primary endpoint of ORR. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.03 (72%/70%), 600 patients will provide more than 90% power to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio) and a 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction (415 out of 600 patients). The response rate for ibrutinib is approximated from published clinical data (Byrd et al 2019).

If the primary objective of non-inferiority of ORR is met, the study will continue until 205 PFS events have occurred. At a 1-sided alpha of 0.025 and a non-inferiority margin of 1.3319 (HR), the power to demonstrate the non-inferiority of zanubrutinib to ibrutinib in PFS is 80%. If the 600 patients are randomized in a 1:1 ratio to the 2 arms over a 24-month period, including a 9-month ramp-up period before reaching peak enrollment of 33 patients/month, with a 0.0017/month hazard rate for drop-out, 205 events are expected to be accumulated at [redacted] months from study start. A median PFS of [redacted] months for ibrutinib, an HR of 0.9, and an exponential distribution for PFS are also assumed.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BTK	Bruton tyrosine kinase
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CT	computed tomography
CYP	cytochrome P450
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire
EQ-5D-5L	European quality of life 5-dimensions 5-levels health questionnaire
FDA	Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
IGHV	immunoglobulin variable region heavy chain
IRB	Institutional Review Board

Abbreviation	Definition
IRT	Interactive Response Technology
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
[redacted]	[redacted]
PR	partial response
PR-L	partial response with lymphocytosis
PRO	patient-reported outcome
R/R	relapsed/refractory
SAE	serious adverse event
SLL	small lymphocytic lymphoma
zanubrutinib	BGB-3111

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 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 a treatable but essentially incurable disease. Diagnosis of CLL requires the presence of ≥ 5000 B lymphocytes/µL in the peripheral blood for at least 3 months with clonality of the circulating B lymphocytes confirmed by flow cytometry. The leukemia cells are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Presence of a cytopenia caused by a typical marrow infiltrate defines the diagnosis of CLL regardless of the number of peripheral blood B lymphocytes or lymph node involvement. Diagnosis of SLL requires the presence of lymphadenopathy and absence of cytopenia caused by a clonal marrow infiltrate. The number of B lymphocytes in the peripheral blood should also not exceed 5000/µL for SLL. CLL cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin are characteristically low compared to those found on normal B cells, with each clone of leukemia cells restricted to expressing either kappa or lambda immunoglobulin light chains (Moreau et al 1997; Ginaldi et al 1998; Hallek 2017).

Genomic landscaping of CLL has revealed that the disease may often be initiated by the loss or addition of large chromosomal elements, eg, deletion 13q (~ 55%), deletion 11q (~ 25%), or trisomy 12 (10% to 20%), followed by additional mutations that may render the leukemia more aggressive (Landau et al 2015). Deletions of the short arm of chromosome 17 (del17p) are detected in 5% to 8% of chemotherapy-naïve patients and almost always include band 17p13 where the tumor suppressor gene TP53 is located. Patients with the del17p clone tend to show marked resistance against genotoxic chemotherapies that cannot be overcome by the addition of anti-CD20 antibodies (Hallek et al 2010; Seiffert et al 2012). In addition to these mutations, additional recurrently mutated genes and somatic copy number variations have also been identified including NOTCH1, MYD88, TP53, ATM, SF3B1, FBXW7, POT1, CHD2, RPS15, IKZF3, ZNF292, ZMYM3, ARID1A, and PTPN11 (Landau et al 2015; Quesada et al 2011; Puente et al 2011; Puente et al 2015).

Survival of CLL cells is dependent on a permissive microenvironment composed of macrophages, T cells, or stromal follicular dendritic cells providing stimuli for activation of crucial survival and pro-proliferative signaling pathways in transformed cells (Tsukada et al 2002; Pedersen et al 2002; Burger et al 2009; Hallek 2017). This microenvironment produces chemokines, cytokines, and angiogenic factors that can interact with the leukemia cells, providing support for their survival (Burger et al 2009; Chiorazzi et al 2005; Reinart et al 2013; Hallek 2017).

Staging of CLL is typically per either the modified Rai or Binet staging system. Modified Rai defines low-risk disease as those with lymphocytosis with circulating leukemia cells and/or marrow involvement (lymphoid cells > 30%) (formerly Rai stage 0). Patients with lymphocytosis, lymphadenopathy, splenomegaly, and/or hepatomegaly are categorized as intermediate-risk disease (formerly Rai stage I or II), whereas high-risk disease includes patients with disease-related anemia (hemoglobin [Hgb] < 11 g/dL) and/or thrombocytopenia (platelet count < 100 x 10^9/L) (formerly Rai stage III and formerly Rai stage IV, respectively) (Rai et al 1975). The Binet staging system is based on the number of areas involved, ie, presence of enlarged lymph nodes, organomegaly, or whether there is anemia or thrombocytopenia. Areas of involvement considered include head and neck (including Waldeyer ring), axillae, groins, spleen, and liver. Binet defines stage A as Hgb ≥ 10 g/dL, platelet count ≥ 100 x 10^9/L, and up to 2 involved areas; stage B is Hgb ≥ 10 g/dL, platelet count ≥ 100 x 10^9/L, and organomegaly greater than that defined for stage A (3 or more areas of nodal or organ enlargement); stage C is Hgb < 10 g/dL and/or platelet count < 100 x 10^9/L (Binet et al 1981).

Decision to initiate treatment for CLL/SLL is based upon the presence of progressive or active/symptomatic disease, eg, progressive marrow failure, massive or progressive splenomegaly and/or lymphadenopathy, worsening lymphocytosis with an increase of > 50% over a 2-month period, lymphocyte doubling time of < 6 months, autoimmune complications that respond poorly to corticosteroids or other standard therapies, and/or constitutional symptoms (Hallek et al 2008).

Front-line CLL treatment for those without del17p or TP53 mutations may include combination fludarabine, cyclophosphamide, and rituximab, or bendamustine and rituximab for the frail elderly patients, while for those with del17p or TP53 mutations, ibrutinib (Bruton tyrosine kinase [BTK] inhibitor) or idelalisib (phosphatidyl inositol 3-kinase [Pi3K] delta inhibitor) plus rituximab should be considered. For patients with impaired physical condition such as those with abnormal creatinine clearance and/or a low cumulative illness rating scale score but without del17p or TP53 mutations, treatment with chlorambucil + an anti-CD20 antibody such as obinutuzumab, or single-agent ibrutinib, may be considered. For those with impaired physical condition who have del17p or TP53 mutations, single-agent ibrutinib, alemtuzumab, high-dose rituximab, or ofatumumab would be the preferred treatment options (Bauer et al 2012; Goede et al 2015; Hillmen et al 2015; Hallek 2017; Robak et al 2010).

Second-line treatment for refractory CLL, defined as disease relapse within 6 months after last treatment, or for disease that relapses within 3 years after first remission, may include ibrutinib, idelalisib plus rituximab, venetoclax (BH3-mimetic designed to block the function of the Bcl-2 protein) alone or in combination with an anti-CD20 antibody; alemtuzumab; fludarabine, cyclophosphamide, and rituximab (after bendamustine and rituximab) and vice versa; or lenalidomide. For the suitable patient, allogeneic stem cell transplantation may also be offered. For patients who progress after 3 years from initial remission, the same first-line therapy may be administered again.

1.2. B-cell Receptor Signaling

B-cell receptor signaling is an important component for the survival of CLL cells, with continuous or repetitive B-cell receptor signaling capable of enabling the growth of CLL cells (Petlickovski et al 2005; Stevenson et al 2011). The B-cell receptor signaling in CLL cells is

supported by different tyrosine kinases including BTK, spleen tyrosine kinase, ZAP70, Src family kinases, and Pi3K.

Blockade of the B-cell receptor signaling cascade by inhibition of either BTK (Honigberg et al 2010) or the delta isoform of Pi3K (Zelenetz et al 2017) has been shown to induce profound inhibition of proliferative signaling from CLL cell-host interactions, resulting in frequent and durable responses in patients with both previously untreated and relapsed/refractory (R/R) CLL. While the use of Pi3K delta inhibitors is often limited by toxicities including hepatotoxicity, colitis, and infection complications, particularly when used in combination with other agents (Zydelig® Summary of Product Characteristics) and in previously untreated patients (Falchi et al 2016), the BTK inhibitor ibrutinib has a highly favorable tolerability profile when compared to conventional therapies.

1.2.1. Ibrutinib

Ibrutinib is a small-molecule inhibitor of BTK. Nonclinical studies have demonstrated inhibition of malignant B-cell proliferation and survival by ibrutinib in vivo, as well as cell migration and substrate adhesion in vitro. In patients with recurrent B-cell lymphoma, > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In a Phase 1b/2 study of patients with R/R CLL (n = 85) where 51 patients received ibrutinib at a daily dose of 420 mg and 34 patients received ibrutinib at a daily dose of 840 mg, the overall response rate (ORR) was identical at 71% for both groups of patients. An additional 20% and 15% of patients had partial response (PR) with lymphocytosis (PR-L) in the 2 groups, respectively. The responses observed were independent of clinical and genomic risk factors including del17p. At 26 months, the estimated progression-free survival (PFS) rate was 75%, and the overall survival (OS) rate was 83% (Byrd et al 2013). In another Phase 1b/2 trial that evaluated the combination of ibrutinib with ofatumumab in patients with either R/R CLL/SLL, prolymphocytic leukemia, or Richter's transformation who had failed at least 2 prior therapies, ORR for patients with CLL/SLL was 100%, with estimated 12-month PFS of 89% (Jaglowski et al 2015).

In a Phase 3 study that compared ibrutinib to ofatumumab in patients with relapsed or refractory CLL (RESONATE), at median follow-up of 9.4 months, ibrutinib was found to significantly improve PFS compared to ofatumumab (ibrutinib: median duration not reached; ofatumumab: 8.1 months; $p < 0.001$). Ibrutinib also significantly improved OS, with an OS rate of 90% at 12 months for ibrutinib versus 81% for ofatumumab ($p = 0.005$).

Overall response rate, per independent central review, was 42.6% (PR: 42.6%) for ibrutinib versus 4% (PR: 4%) for ofatumumab; PR-L rate was 20% and 0% for the 2 treatment groups, respectively.

Overall response rate, per investigator review, was 69.7% (complete response [CR]/complete response with incomplete bone marrow recovery [CRi]: 2%; PR: 68%) for ibrutinib versus 21.4% (CR/CRi: 1%; PR: 21%) for ofatumumab; PR-L rate was 15% and 2% for the 2 treatment groups, respectively.

In another Phase 3 study (HELIOS) that compared 6 courses of bendamustine and rituximab in combination with either ibrutinib or placebo (n = 578) in patients with R/R CLL, at a median

follow-up of 17 months, PFS was significantly improved in the ibrutinib group (not reached) versus placebo (13.3 months) ($p < 0.0001$) (Chanan-Khan et al 2016).

Ibrutinib is well tolerated compared with chemotherapeutic treatments for CLL. In the Phase 3 RESONATE study, Grade 3 or higher adverse reactions reported in ≥ 10% of patients treated with ibrutinib were diarrhea (4%), nausea (2%), stomatitis (1%), pyrexia (2%), upper respiratory tract infection (1%), pneumonia (10%), sinusitis (1%), urinary tract infection (4%), rash (3%), musculoskeletal pain (2%), arthralgia (1%), headache (1%), neutrophils decreased (23%), and platelets decreased (5%). For the Phase 3 study comparing ibrutinib to chlorambucil in patients with CLL (RESONATE2), Grade 3 or higher adverse reactions reported in ≥ 10% of patients treated with ibrutinib were diarrhea (4%), stomatitis (1%), musculoskeletal pain (4%), arthralgia (1%), rash (4%), skin infection (2%), pneumonia (8%), urinary tract infections (1%), peripheral edema (1%), hypertension (4%), and headache (1%). Across clinical trials, Grade 3 or higher bleeding events occurred in up to 6% of patients treated with ibrutinib, with bleeding event of any grade including bruising and petechiae occurring in approximately 50% of patients. Atrial fibrillation and atrial flutter occurred in 6% to 9% of patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infection, and a prior history of atrial fibrillation. Other malignancies (3% to 16%) including non-skin carcinomas (1% to 4%) have been observed in patients on ibrutinib. Tumor lysis syndrome has infrequently been reported with ibrutinib therapy. Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman (Imbruvica® US Prescribing Information).

Ibrutinib is currently approved by the United States Food and Drug Administration (FDA) for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy, patients with CLL/SLL with or without 17p deletion, patients with Waldenström macroglobulinemia, patients with marginal zone lymphoma who have received at least 1 prior anti-CD20 based therapy, and patients with chronic graft versus host disease after failure of 1 or more lines of systemic therapy (Imbruvica® US Prescribing Information).

1.2.2. Zanubrutinib

Zanubrutinib (also known as BGB-3111) is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacologic and pharmacokinetic (PK) profile. Zanubrutinib is different from ibrutinib in the following ways:

- Zanubrutinib is more selective 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;
- Zanubrutinib has improved oral bioavailability;
- Zanubrutinib displays significantly less inhibitory effect on rituximab-induced antibody-dependent cell-mediated cytotoxicity, and so is unlikely to adversely impact the anti-tumor effects of rituximab.

1.2.2.1. Nonclinical Data for Zanubrutinib

Summaries of nonclinical studies are provided below. [redacted]

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 phospholipase C gamma 2 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 to 20 nM, while it was inactive in many other hematologic cancer cell lines.

In vivo studies have demonstrated that zanubrutinib induces dose-dependent anti-tumor 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 anti-tumor activity than ibrutinib in a TMD-8 diffuse large B-cell lymphoma subcutaneous xenograft model. In a PK/pharmacodynamics 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.

[redacted] 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 corrected QT interval (QTc) changes were noted in the conscious telemetry-implanted dogs over 24 hours after dosing up to 100 mg/kg, or in the repeat dose toxicity studies in dogs over 91 days at doses up to 100 mg/kg/day. No mortality or severe toxicity was noted in 91-day repeat dose toxicity studies in both rats and dogs at doses up to 300 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.

1.2.2.2. Summary of Relevant Clinical Experience with Zanubrutinib

Dose Selection for Zanubrutinib

In the first-in-human, Phase 1 study, BGB-3111-AU-003, the PK of zanubrutinib was linear between 40 and 320 mg orally once daily [redacted]
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

daily. Results from a food effect study showed that zanubrutinib exposure was not altered by a 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 daily 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, Waldenström 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 daily and 320 mg once daily 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 daily has been selected as the recommended Phase 3 dose based on sustained target occupancy, high rates of objective response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

Preliminary Efficacy and Safety Data for Zanubrutinib in CLL/SLL Patients

As of 16 September 2018, 123 patients with CLL/SLL have been enrolled in the BGB-3111-AU-003 study (first-in-human, Phase 1). Zanubrutinib was well tolerated, with 23.6% of patients reporting no drug-related adverse events (AEs) > Grade 2 severity. The most frequent AEs of any attribution were contusion (54 patients; 43.9%), upper respiratory tract infection (36.6%), diarrhea (26.8%), cough (25.2%), headache (20.3%), and fatigue (18.7%). There were 49 patients (39.8%) that experienced at least one SAE, the most frequent included pneumonia (5.7%), febrile neutropenia (1.6%), neutropenia (1.6%), urinary tract infection (1.6%), lower respiratory tract infection (1.6%), arthralgia (1.6%), and cellulitis (1.6%). Of these SAEs, 18 (14.6%) were assessed as possibly related to zanubrutinib. [redacted]

Efficacy for CLL/SLL patients from the BGB-3111-AU-003 trial was last reported for a data cut of 31 March 2017 (Seymour et al, 2017). For the 66 patients evaluable for efficacy, after a median follow-up of 10.5 months (range, 2.2 to 26.8 months), the ORR was 94% (62/66), with partial response (PR) rate of 82% (54/66), partial response with lymphocytosis rate of 9% (6/66), and stable disease (SD) rate of 5% (3/66). The response rate to zanubrutinib therapy in previously untreated patients (n = 16) was 100% (16/16 with 1 complete response [CR], 13 with PR and 1 with partial response with lymphocytosis).

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 electrocardiogram (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.

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that coadministration of zanubrutinib with the strong cytochrome P450 (CYP) 3A 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. Co-administration 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.

Additionally, a preliminary physiologically-based pharmacokinetic (PBPK) model was developed and was used to predict the effect of moderate 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 and 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 show that zanubrutinib does not significantly affect drugs metabolized by CYP2C9 (warfarin) or transported by BCRP (statins). Zanubrutinib has 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}.

1.2.2.3. Benefit-Risk Assessment

As of 16 September 2018, approximately [redacted] patients have received zanubrutinib in completed and ongoing clinical trials evaluating zanubrutinib either as monotherapy or in combination with another agent. Available data for zanubrutinib in patients with CLL/SLL support a positive benefit-risk profile for the use of zanubrutinib as an investigational agent for treatment of CLL/SLL.

2. STUDY OBJECTIVES

Primary:

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by overall response rate determined by investigator assessment

Secondary:

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
  - Progression-free survival determined by investigator assessment and independent central review
  - Overall response rate determined by independent central review
  - Duration of response as determined by independent central review
  - Duration of response as determined by investigator assessment
  - Time to treatment failure
  - Rate of partial response with lymphocytosis or higher determined by independent central review
  - Overall survival
  - Patient-reported outcomes
- To compare the safety of zanubrutinib versus ibrutinib

[redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 3, randomized study of zanubrutinib versus ibrutinib in approximately 600 patients with R/R CLL/SLL. The primary efficacy endpoint is ORR determined by investigator assessment. While the primary efficacy endpoint is per investigator assessment, ORR per independent central review will also be analyzed to support the primary analysis. In the United States, ORR assessed by independent central review will be the basis for regulatory decisions. Disease response will be assessed per the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2), and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL (Appendix 3). Rate of PR-L or higher will be assessed as a secondary efficacy endpoint considering the finding that treatment with BTK inhibitors may lead to lymphocytosis due to redistribution of leukemia cells from lymphoid compartment to blood. In these instances, treatment-related transient progressive lymphocytosis is not a sign of treatment failure or disease progression and has no bearing on treatment outcome (Woyach et al 2014).

The study is broken into three periods for every patient:

- Screening Period (Section 5.2)
- Treatment Period (Section 5.11)
- Post-Treatment Period
  - End of Treatment Visit (Section 5.12.1)
  - Long-Term Follow-up (Section 5.12.2)
  - Survival Follow-up (Section 5.12.3)

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent). For the purposes of stratification, refractory disease is defined as either no objective response or disease progression within 6 months of the last CLL/SLL treatment, and relapsed disease is defined as patients whose disease relapses more than 6 months after the last CLL/SLL treatment and subsequently progressed.

Treatment with zanubrutinib and ibrutinib will be open label. Study treatment will continue until disease progression, or any of the events outlined in Section 6.7. The study duration is estimated to be approximately [redacted] months (see Section 3.5).

Study Assessments:

The timing of all study assessments is described in Appendix 10. Assessments to be performed during the study include:

- [redacted]
- Disease-related constitutional symptoms (Section 5.6.1)
- Physical examination of liver, spleen, and lymph nodes (Section 5.6.2)
- Computed tomography (CT) scan of neck, chest, abdomen, and pelvis with contrast (see Section 5.6.3 for details)
- Bone marrow examination at screening, for patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CRi, [redacted] (see Section 5.6.4 for details)
- Patient-reported outcomes (PROs) including the European quality of life 5-dimensions 5-levels health questionnaire (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire (EORTC QLQ-C30). [redacted] (see Section 5.7).
- Laboratory studies including hematology, serum chemistry, serum immunoglobulins, coagulation, hepatitis B and C, pregnancy, and HIV (See Sections 5.8)
- Biomarkers blood and bone marrow samples to investigate genetic alterations in the tumor cells such as del17p, del11q, 12q+, and immunoglobulin variable region heavy chain (IGHV) mutation analysis [redacted] (see Section 5.9)

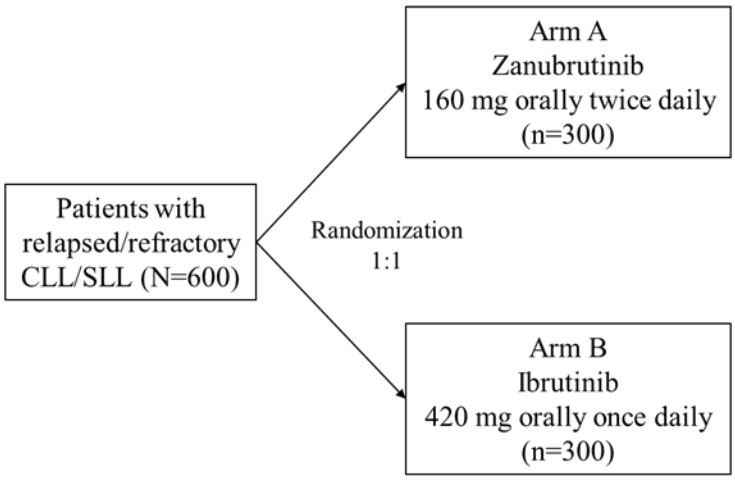
Patients should remain on study treatment until disease progression is confirmed by independent central review (as described in Section 6.7).

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, electrocardiogram (ECG), and vital signs (Section 5.5). AEs will be graded for severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 and the Grading Scale for Hematologic Toxicities in CLL Studies (see Section 8.1.1.1). An independent Data Monitoring Committee (DMC) will periodically monitor safety data (see Section 10.2).

Efficacy (Section 5.6) will be assessed locally by the investigator as well as by independent central review (Section 10.3). Progression must be confirmed by independent central review (Section 6.7).

3.2. Study Schema

Figure 1: Study Schema



Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present versus absent).

3.3. Blinding

Treatment with zanubrutinib and treatment with ibrutinib will be open label; however, the assessment of ORR by independent central review (primary endpoint) will be blinded.

3.4. Study Rationale

B-cell receptor signaling regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival (Advani et al 2013). It also plays an important role in survival of CLL cells. BTK has a relevant role in the signal transduction of B-cell receptor and can lead to downstream activation of cell survival pathways such as NF-κB and MAP kinases via the Src family kinases. Ibrutinib, an FDA-approved first-generation BTK inhibitor that blocks B-cell receptor signaling in human B cells via specific active site occupancy, has been shown to be efficacious and tolerated in the treatment of CLL/SLL.

In the Phase 3 RESONATE study that compared ibrutinib to ofatumumab in patients with relapsed or refractory CLL/SLL, ORR (PR or higher) per independent central review was 42.6% (PR: 42.6%) for ibrutinib, whereas per investigator review, ORR was 69.7% (CR/CRi: 2%; PR: 68%) for ibrutinib (Byrd et al 2014). Across ibrutinib clinical trials, Grade 3 or higher bleeding events occurred in up to 6% of patients treated with ibrutinib, with bleeding event of any grade including bruising and petechiae occurring in approximately 50% of patients. Atrial fibrillation and atrial flutter occurred in 6% to 9% of patients treated with ibrutinib (Imbruvica® U.S. Prescribing Information).

[redacted]

[redacted]

Treatment with zanubrutinib has been well tolerated across all studies thus far. Compared to ibrutinib, zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, henceforth possibly leading to reduced toxicities due to off-target inhibition such as diarrhea, thrombocytopenia, bleed, atrial fibrillation, rash, and fatigue. [redacted]

Based on the preliminary data from BGB-3111-AU-003, the efficacy of zanubrutinib in the treatment of CLL/SLL [redacted] is hypothesized to at least be non-inferior to ibrutinib (PR or higher [RESONATE]: 69.7% per investigator review; 42.6% per independent central review). Preliminary safety data from the BGB-3111-AU-003 study also revealed a tolerable and safe profile for zanubrutinib, with possibly a lower rate of Adverse Event of Interest such as atrial fibrillation and bleed when compared with ibrutinib. In view of these findings, a Phase 3 non-inferiority study comparing the efficacy of zanubrutinib and ibrutinib measured by ORR, the primary endpoint, will be conducted.

3.5. Duration of Study

The total duration of this study is expected to be approximately [redacted] months based on assuming an expected enrollment duration of [redacted] months, and an estimated follow up of [redacted] months after the last patient is enrolled.

3.5.1. Study Drug Access at Study Closure

Patients, who in the opinion of the investigator, continue to benefit from study treatment with either zanubrutinib or ibrutinib may continue treatment with zanubrutinib after study closure by enrolling in the Zanubrutinib Long-Term Extension Study. This study is a rollover study for patients who wish to continue receiving zanubrutinib, which will continue to be supplied until the patient progresses.

4. ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

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

1. Age 18 years or older
2. Confirmed diagnosis of CLL or SLL that meets the IWCLL criteria (Hallek et al 2008)
3. CLL/SLL requiring treatment as defined by at least 1 of the following criteria:
    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 x 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. 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
        iii. Fevers > 100.5ºF or 38ºC for ≥ 2 weeks without other evidence of infection.
        iv. Night sweats for > 1 month without evidence of infection
4. Relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL. A line of therapy is defined as completing at least 2 cycles of treatment of standard regimen according to current NCCN or ESMO guidelines, or of an investigational regimen on a clinical trial.
5. Measurable disease by CT/magnetic resonance imaging (MRI). Measurable disease is defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters or an extranodal lesion must measure > 10 mm in longest perpendicular diameter (LPD).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
7. Life expectancy ≥ 6 months

8. Adequate bone marrow function as defined by:
    a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 (growth factor use is allowed), except for patients with bone marrow involvement in which case ANC must be ≥ 750/mm^3
        - 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 and at least 7 days following the most recent administration of other myeloid growth factors (eg, G-CSF, GM-CSF)
    b. Platelet ≥ 75,000/mm^3 (may be post-transfusion), except for patients with bone marrow involvement by CLL in which case the platelet count must be ≥ 30,000/mm^3
    c. Hemoglobin ≥ 7.5 g/dL (may be post-transfusion)
9. 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 unless due to CLL/SLL
    c. Serum total bilirubin < 3.0 × upper limit of normal (unless documented Gilbert's syndrome)
10. Female patients of childbearing potential must practice highly effective methods (Section 5.2.1) of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
11. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception with other highly effective methods described in Section 5.2.1 during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
12. Ability to provide written informed consent and can understand and comply with the requirements of the study.

4.2. Exclusion Criteria

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

1. Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation (biopsy based on clinical suspicion may be needed to rule out transformation)
2. 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 (Appendix 4)
    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes)
    e. QTcF > 480 milliseconds based on Fridericia's formula

   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 mmHg and diastolic blood pressure > 105 mmHg at screening

3. 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
4. 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
5. History of stroke or intracranial hemorrhage within 180 days before first dose of study drug
6. Severe or debilitating pulmonary disease
7. Unable to swallow study drug, 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
8. Active fungal, bacterial, and/or viral infection requiring systemic therapy
9. Known central nervous system involvement by leukemia or lymphoma
10. 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
11. Known infection with HIV or serologic status reflecting active viral 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 (< 20 IU), and if they are willing to undergo monitoring for HBV reactivation
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable
12. Moderate or severe hepatic impairment, ie, Child-Pugh class B or C
13. Major surgery within 4 weeks of the first dose of study drug
14. Prior treatment with a BTK inhibitor
15. Last dose of prior therapy for CLL/SLL ≤ 14 days before randomization, with the following additional exclusion requirements:
    a. Treatment with monoclonal antibody-based therapy within 28 days of first dose of study drug
    b. Treatment with chimeric antigen receptor T-cell therapy within 180 days of first dose of study drug

c. Treatment with Chinese herbal medicine with anticancer intent within 28 days of first dose of study drug
d. Chemotherapy or radiation treatment within 21 days of first dose of study drug or hematopoietic stem cell transplantation within 90 days of first dose of study drug

16. Ongoing need for corticosteroid use during the trial. NOTE: systemic corticosteroids must be fully tapered off/stopped at least 5 days before the first dose of study drug
17. Toxicity from prior anticancer therapy that has not recovered to ≤ Grade 1 (except for alopecia, ANC, and platelet count; for ANC and platelet count, see inclusion criterion 8)
18. Pregnant or lactating women
19. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
20. Ongoing alcohol or drug addiction
21. Hypersensitivity to zanubrutinib, ibrutinib, or any of the other ingredients in either drug
22. Patient requires treatment with warfarin or other vitamin K antagonists
23. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
24. Concurrent treatment for CLL/SLL outside of this clinical trial (includes the screening period)
25. Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (eg, idiopathic thrombocytopenia purpura) requiring treatment.

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 Schedule of Assessments (Appendix 10).

5.1. Study Visit Schedule

Scheduled study visits are outlined in the Schedule of Assessments (Appendix 10). The study visit schedule is based around 28-day cycles, with visits expected to occur in D1 of a given cycle. The length of a cycle should remain 28-days regardless of any drug holds occurring during that cycle. Acceptable windows around these visits are indicated in Appendix 10: a visit window of ± 6 days (ie, 6 days before or after the given day) can be assumed for any cases not otherwise specified in the Schedule of Assessments (Appendix 10). Study drug supply (Section 6.1.3) and dispensation (Section 6.1.4) must be taken into account when scheduling study visits. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2. Screening

Before screening procedures are conducted, the patient must sign an informed consent form (ICF). Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the ICF will be given to the patient to read, and the patient must have adequate time to understand the content 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. Consent must be obtained using the most current version of the form approved by the Independent Ethics Committee (IEC).

A patient may sign the informed consent form without starting the screening window; the screening window will start with the first protocol-required screening procedure.

All screening procedures must be performed within the screening window (35 days), unless noted otherwise; assessments not completed within this interval must be repeated. Repeating screening procedures or tests are allowed once 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.

Patients who provide informed consent and meet all eligibility criteria should be randomized to the trial (Section 5.2.5).

5.2.1. 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
  - 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 (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- 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 or ibrutinib. 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.

If patient is using hormonal contraceptives such as birth control pills or devices, a barrier method of contraception (eg, condoms) must also be used.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal 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.

5.2.2. 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 by site starting with the lowest number.

Once a patient number has been assigned to a patient, it cannot be re-assigned to any other patient.

5.2.3. Medical and Cancer History

Review all medical and cancer history after obtaining informed consent, including presence or absence of disease-related constitutional symptoms. Clinically significant medical history (ie, previous diagnoses, diseases, or surgeries) that does not pertain to the study indication, started before signing the informed consent, but considered relevant to the patient's study eligibility will be collected and captured in the electronic case report form (eCRF). "Clinically significant" is defined as any event, diagnosis, or laboratory value requiring treatment or 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, year of birth [or age], and race/ethnicity) will also be collected.

Record non-serious AEs during the screening period as medical history.

5.2.4. 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. No eligibility waiver 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 the medical monitor or designee will provide final approval for enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Authorization Packet is in the patient's file before proceeding with study procedures.

After a patient is randomized, refer to concomitant therapies (Section 7) and study drug discontinuation (Section 6.7) for guidance on a patient's eligibility for treatment.

5.2.5. Enrollment/Randomization

Study treatment should commence within 5 days after randomization, although small extensions to this due to drug supply logistics are permissible with Sponsor approval. Interactive Response Technology (IRT) will be used to randomize patients to treatment arm and to assign study drug as applicable (see Section 6.1.3).

5.3. Study Drug Dispensation

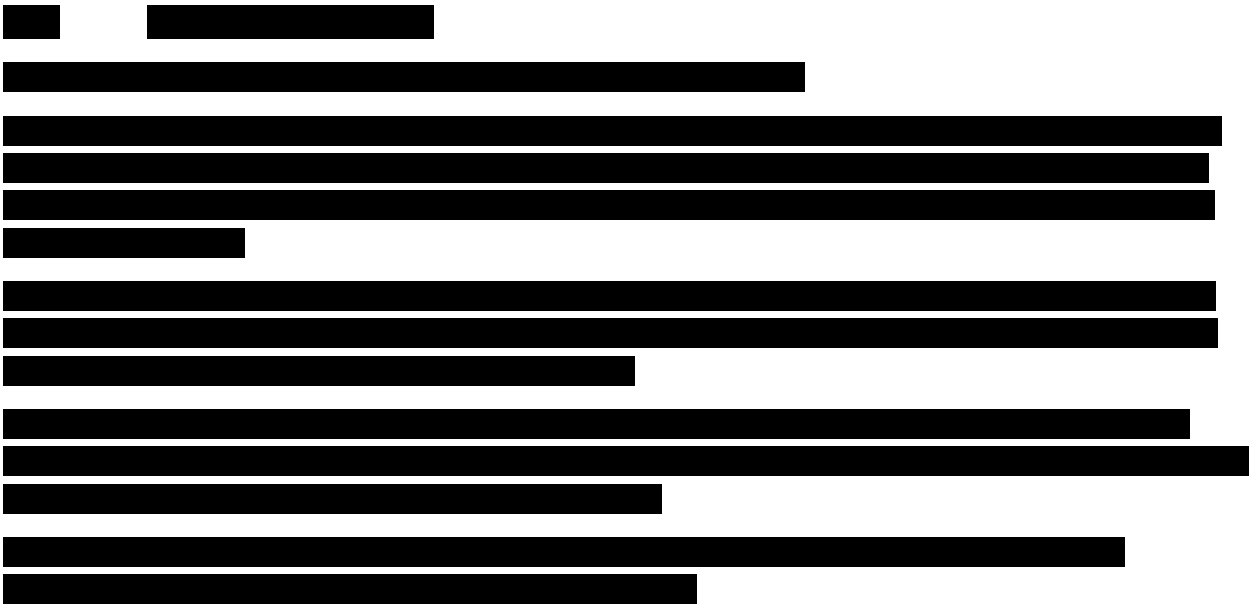
At visits where study drug dispensation occurs, study center personnel should ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the pharmacy manual. Drug may be dispensed as frequently as once every 28-day cycle, but may be modified to less frequently depending on supply considerations throughout the trial (consult the most recent pharmacy manual).

Study patients should be instructed to bring all drug bottles to their study visits, and drug accountability should be performed at each visit (see Section 6.1.4 and Section 5.6.1 for further detail).

Additional drug dispensation visits may occur to ensure a patient has sufficient supply to maintain drug administration compliance as per protocol. The investigator is to instruct the patient to take the study drug exactly as prescribed and at approximately 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 in order for the study staff to perform drug accountability. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

For dispensation of study drug provided by the sponsor, please ensure that the bottle number(s) listed in IRT matches what is being given to the patient.

For drug that is locally procured, please ensure that the lot number dispensed is being recorded on the accountability log.



5.5. Safety Assessments

5.5.1. Cardiac Function

An assessment of left ventricular ejection fraction will be performed and documented at Screening and as medically indicated. Note: An echocardiogram, multigated acquisition, and gated heart pool scan are all acceptable.

5.5.2. Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, heart rate, and body temperature), weight, and review for arrhythmia signs/symptoms (eg, shortness of breath, dizziness, or fainting) will be performed at each study visit during study treatment and at the End of Treatment Visit. Height (cm) is determined at Screening only. Assessment of vital signs and a

focused physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days.

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

5.5.3. ECOG Performance Status

ECOG performance status (Appendix 6) will be assessed at the Screening visit, each visit during study treatment, and at the End of Treatment Visit.

5.5.4. Electrocardiogram

A 12-lead ECG will be performed locally in triplicate at screening for all subjects. During study treatment, ECGs will be performed as specified per the Schedule of Assessments (Appendix 10). Subjects should be in the semi-recumbent or supine position.

5.5.5. Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within the screening window (see Section 5.2), and on study thereafter.

5.5.6. Adverse Events Review

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

Collect non-serious AE information from the time of first dose of study drug through End of Treatment Visit. Information on all SAEs (regardless of relatedness) will be collected from the time of signing of informed consent through screen failure or End of Treatment. 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, and the definition of an SAE is provided in Section 8.2.1. Important additional requirements for reporting SAEs are explained in Section 8.

In addition, arrhythmia signs/symptoms will be reviewed at every visit. This will involve the investigators asking subjects for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness, or fainting) as part of the routine AE monitoring for each visit.

5.6. Efficacy Assessments

Overall response to study treatment will be assessed at the timepoints outlined in Appendix 10. Overall response will be determined as follows:

- CLL: IWCLL criteria (Hallek et al 2008) with addition of treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2)
- SLL: the Lugano Classification for NHL (Cheson et al 2014) for patients with SLL using CT-based response criteria (Appendix 3)

The primary endpoint of this trial is ORR. Assessments relevant to response assessment will be submitted to the central review vendor (Section 10.3). Investigators will also assess overall response locally: refer to Appendix 2 and Appendix 3 for the individual assessments used to determine response and the guidelines on how to integrate them into a single overall response assessment for a given timepoint. Confirmed, unequivocal progression may require discontinuation of study treatment (see Section 6.7).

Assessments relevant to determining a patient's overall response to study drug at a given time point are detailed below. Parameters relevant to response assessment may also include laboratory assessments as detailed in Section 5.8.

An additional early response assessment visit to confirm overall response may be performed in addition regularly scheduled visits as indicated in Appendix 10.

5.6.1. Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms based on IWCLL criteria (Hallek et al 2008) (unexplained fever of ≥ 38ºC; unexplained, recurrent drenching night sweats; or unexplained loss of > 10% body weight within the previous 6 months) will be evaluated as specified per the Schedule of Assessments (Appendix 10).

5.6.2. Physical Examination of Liver, Spleen, and Lymph Nodes

Record presence and extent of hepatomegaly, splenomegaly, and/or lymphadenopathy as specified per the Schedule of Assessments (Appendix 10). PD assessed by physical examination must be confirmed by a CT scan.

5.6.3. Computed Tomography

All patients must have baseline CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites as specified in Appendix 10.

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.

An MRI may be used in place of CT only for patients who have a contraindication to CT scans. If used, MRI should be performed of neck, abdomen, pelvis, and any other disease sites. In addition to the MRI, a non-contrast CT of the chest should be performed. In Germany, an MRI may be used in place of CT for all patients but CT with contrast is still preferred.

CT or MRI will be performed as specified per the Schedule of Assessments (Appendix 10), independent of possible study drug hold.

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 10 mm in at least 1 dimension. Up to 6 of the lesions with bi-dimensional measurements will be identified as 'target' lesions. From the remaining measurable lesions, up to 6 Non-Index lesions may be selected and followed qualitatively throughout the course of the study. 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: longest diameter (LDi) and short diameter (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
- All bone lesions, irrespective of the modality used to assess them
- Cutaneous lesions
- Gastrointestinal disease
- Spleen, liver, kidneys
- Irradiated lesions
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites

At each imaging timepoint, lesions (nodal and nonnodal) 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 should be indicated as "too small to measure" in the electronic data capture system (EDC). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

All CT scans and MRIs obtained during the study will be collected and reviewed by a central imaging vendor identified for this trial. De-identified copies of all scans and radiology reports (including those from Screening) must be provided to the sponsor or designee (eg, central imaging vendor).

5.6.4. Bone Marrow Examination

The schedule of required bone marrow examinations is given in Appendix 10. Details on these examinations and when they are required are given below:

Bone Marrow Biopsy

- In lieu of performing a bone marrow procedure, a site can submit any of the following from a previously performed diagnostic bone marrow biopsy if it is obtained within 90 days before randomization:
  - an archival block
  - 15 unstained slides

- At the time of potential CR or CRi.
  - Patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CRi, and need bone marrow examination to confirm CR or CRi. This should be collected within 40 days from the CT/MRI meeting the criteria of CR or CRi. All the other clinical data should be within ± 14 days from the CT/MRI (ie, complete blood count [CBC] with differential and physical examination.
    - Patients who are otherwise complete responders but show bone marrow involvement preventing CR/CRi classification should recheck bone marrow at least once every 12 months until CR or CRi is confirmed as long as the patient is still showing evidence of being CR or CRi outside of bone marrow results. Recheck may be done earlier than 12 months as clinically indicated

[redacted]

Bone Marrow Aspirate

- At Screening, for patients with SLL, for biomarker purposes (see Section 5.9). This must be a fresh sample within the screening window.
- At time of potential CR or CRi to confirm response (see guidance for bone marrow biopsy for timing) [redacted]

[redacted]

All bone marrow samples will be collected and reviewed by a pathologist from the central pathology laboratory.

5.7. Patient-Reported Outcomes

Patients should complete the PROs per the Schedule of Assessments (Appendix 10) before study drug is administered and prior to performing any other procedures.

5.7.1. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The EuroQol 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.

5.7.2. 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 3000 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 NHL 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.

[redacted]

5.8. Laboratory Assessments

Laboratory assessments required during the trial are detailed below.

Laboratory assessments will be performed at the timepoints specified in the Schedule of Assessments (Appendix 10) and may also be performed as medically necessary. On Cycle 1 Day 1 (day of first dose of study drug), laboratory assessments should be done before the first study drug administration. If local laboratories are being used, screening laboratory assessments performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1.

Study Central Laboratories versus Local Laboratories

If not otherwise specified below, laboratory assessments may be done at the study central laboratory or at the site's local laboratory. The method used at baseline for a given patient should be used throughout the rest of the trial. For a specific visit, if there is an issue with that method the other method may be substituted (ie, if a patient was using central laboratories since baseline but on the most recent visit the sample is lost, the site can enter local laboratories into the EDC for that visit).

If the study central laboratory is used, a detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all materials such as test tubes and labels is provided in the laboratory manual.

If the study central laboratory is used, local laboratories may still be used for patient safety and monitoring. In these cases, a specific local laboratory only needs to be entered in the EDC if it is relevant to study actions or data (ie, if local labs are triggering a dose interruption, modification, or resulting in a reported adverse event). If the central lab adequately reflects study actions and data, then there is no requirement to enter local labs into the EDC.

[redacted]

5.8.1. Hematology

CBC with differential includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil).

5.8.2. Serum Chemistry

Serum chemistry includes sodium, potassium, chloride, bicarbonate (carbon dioxide, or if neither is available carbon dioxide combining power), glucose, blood urea nitrogen (or serum urea), creatinine, calcium, phosphate (or phosphorus), magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase.

The following 2 chemistry tests will only be done at Screening and will be performed locally: direct antiglobulin test and β-2 microglobulin.

5.8.3. Serum Immunoglobulins

Quantitative serum immunoglobulins (IgG, IgM, and IgA) will be measured.

5.8.4. 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 and as clinically indicated.

5.8.5. Hepatitis B and C testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening via study central laboratory.

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 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 who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo HBV DNA monitoring by PCR at least once on every cycle. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every 90 days (every third cycle). HBV DNA at screening or for monitoring may be done locally if local testing sensitivity is adequate and after discussion with the medical monitor.

If, during monthly monitoring of HBV DNA by PCR, the value is between 20 and < 100 IU/mL, then the HBV DNA by PCR should be rechecked within 2 weeks. If the value is 100 IU/mL or greater, or at rechecked a detectable copy number, then study drug should be stopped and antiviral therapy initiated or continued. 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 monitoring per cycle/every 4 weeks. HCV RNA at screening or for monitoring may be done locally if local testing sensitivity is adequate and after discussion with the medical monitor. 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.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation. Table 1 describes how the results for HBV and HCV testing at screening relate to study eligibility

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 during every cycle*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not detected"* *Perform monitoring of HCV RNA during every cycle*	**Antibody (+)** *HCV RNA detected*

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

5.8.6. 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. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Day 1 of every cycle and for at least 90 days after the last dose of study drug. 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 participation in the study.

5.8.7. HIV Testing

Subjects with HIV infection are excluded from the study. HIV testing will be performed during Screening unless previous HIV test results from ≤ 4 weeks prior to Screening are available.

5.9. Biomarkers

Samples for biomarkers will be collected as indicated in Appendix 10. Details on these samples and when they are required are given below.

5.9.1. Del17p and Cytogenetics

CLL/SLL is characterized by various mutations shown to be linked to favorable prognosis (del13q and hypermutation of IGHV) or poor prognosis (del17p, del11q, unmutated IGHV, mutations in TP53, ATM, and Notch1).

Screening blood samples will be used for the assessment of prognostic biomarkers including the assessment of chromosomal abnormalities (del17p, del11q, and the marker D13S319 on chromosome 13q, and to determine trisomy 12) by fluorescence in situ hybridization (FISH) using a specialized central laboratory.

Screening bone marrow samples will also be collected for patients with SLL (Section 5.6.4), for central del17p FISH testing.

[redacted]

5.9.3. TP53 Mutation and Other Molecular Analysis

Blood samples will also be collected for the assessment of the mutation status of relevant genes by molecular techniques including, but not limited to, TP53, IGHV, Notch, etc, as indicated in Appendix 10. [redacted]

5.10. 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; and hematology and chemistry laboratory assessments. 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.

5.11. Treatment Period

The treatment period starts with the first day of assigned study treatment and ends 30 days following date of permanent study drug discontinuation (ie, 30 days after the final administered dose of zanubrutinib or ibrutinib)

Patients may discontinue study drug treatment for any one of the reasons presented in Section 6.7. Patients that end treatment should move on to the End of Treatment Visit.

Patients may voluntarily withdraw consent for treatment at any time.

5.12. Post-Treatment Period

5.12.1. End of Treatment

All patients who permanently discontinue study drug will have an End of Treatment 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 investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information. Refer to the Schedule of Assessments (Appendix 10) for the assessments to be performed at the End of Treatment Visit. This visit should signify the patient's transition to Long-term Follow-up (if they have yet to progress) or Survival Follow-up (if they have already progressed).

5.12.2. Long-term Follow-up

All patients who discontinue study drug treatment and have yet to have documented and confirmed progression by independent central review will remain in the study and subsequently commence Long-term Follow-up, which includes monitoring survival status, subsequent therapies for CLL/SLL, and overall response assessments (including radiographic imaging) to monitor for disease progression. Refer to the Schedule of Assessments (Appendix 10) for the assessments to be performed at the Long-term Follow-up Visits.

If the patient refuses to return for these visits or is unable to do so, every effort should be made to contact him/her or the patient's guardian by telephone to determine the patient's disease status and survival.

Patients who have documented and confirmed progression by independent central review during Long-term Follow-up should move to Survival Follow-up.

5.12.3. Survival Follow-up

Patients who have discontinued study treatment and have documented and confirmed progression by independent central review should enter Survival Follow-up, which consists of monitoring for survival status and subsequent therapies for CLL/SLL. There are no mandatory study visits during Survival Follow-up: information may be confirmed via a phone call, medical records, or other methods. Patients should continue in Survival Follow-up until the end of the study.

5.13. 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

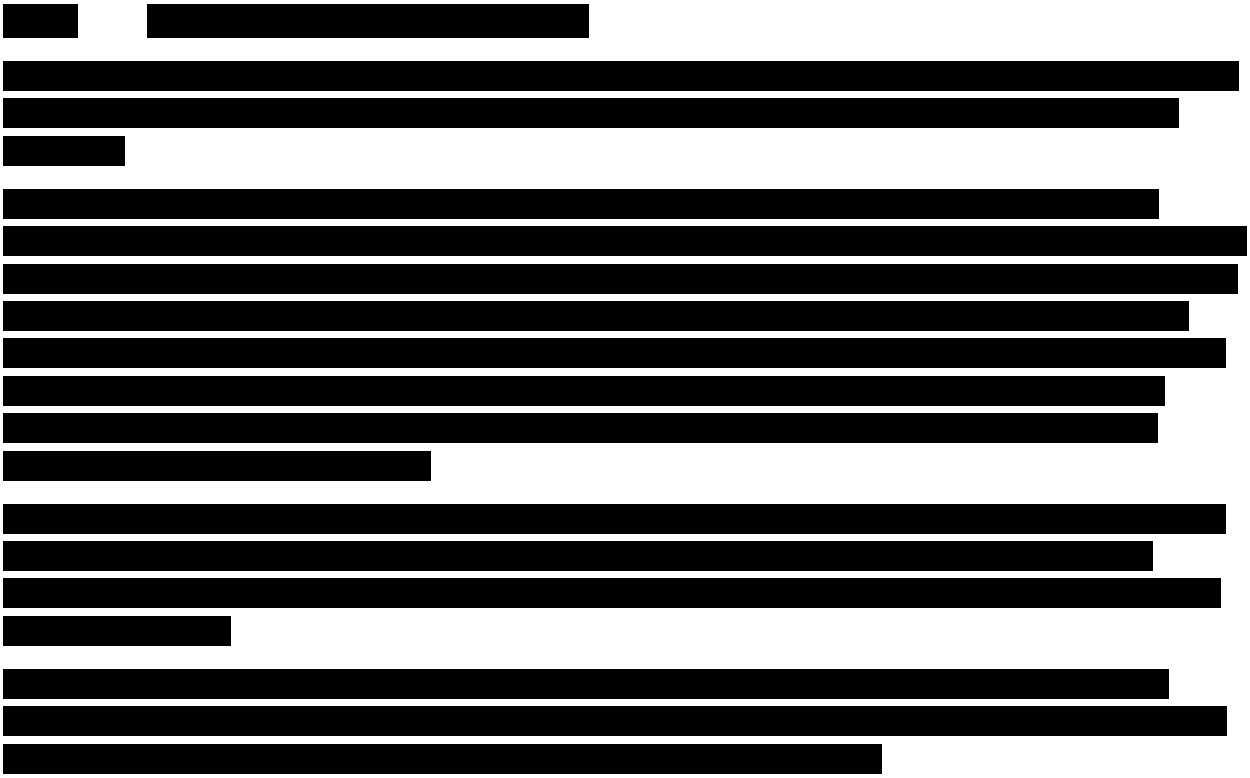
The patient may elect to withdraw from the study for reasons other than those listed above - any other reasons need to be documented and explained in the eCRF. Patients may voluntarily withdraw consent from the study at any time.

5.14. Lost to Follow-up

Every reasonable effort should be made to contact any patient 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 to establish contact fail, 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 bottle with an induction seal and bottle label. Commercial supplies of ibrutinib will either be provided by the sponsor or directly purchased via local procurement by the site.

Refer to the pharmacy manual for specifics on packaging and label content.

The contents of the label will be in accordance with all applicable local regulatory requirements.

6.1.2. Handling and Storage

The Interactive Response Technology (IRT) system will be used for drug supply management. Sponsor-supplied study drug(s) 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 (59ºF to 86ºF).

The storage conditions for ibrutinib are found on the local drug label. Retain in original package until dispensing.

6.1.3. Study Drug Supply

Zanubrutinib capsules will be provided by the sponsor.

Ibrutinib will be provided via local procurement by the site. In limited circumstances, they may be provided by the sponsor.

6.1.4. Study Drug Dispensation Procedures

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).

Study drug will be dispensed by the study center personnel to patients to ensure adequate drug supply for administration at home throughout the treatment phase. Visits for dispensation should occur no less frequently then at every scheduled study visit (see Appendix 10) on this trial.

The investigator is to instruct the patient to take the study drug exactly as prescribed and at approximately the same time on 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

dispensed to the patient and all dose changes, including reason for dose changes, during the study must be recorded on the appropriate eCRF.

For dispensation of study drug provided by the sponsor, please ensure that the bottle number(s) listed in IRT matches with what is being given to the patient.

For drug that is locally procured, please ensure that the lot number dispensed is being recorded on the accountability log.

6.1.5. 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.

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. 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, the amount supplied, and/or the amount administered to and returned by patients, if applicable.

6.1.6. 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 (or designee) approval.

6.2. Dosage and Administration

6.2.1. Zanubrutinib

Zanubrutinib 160 mg will be taken 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. In case of dose reduction (See Section 6.5.1), the number of capsules taken at each administration will be reduced.

Patients randomized to Arm A (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.

[redacted]

6.2.2. Ibrutinib

Patients randomized to Arm B will receive ibrutinib. Ibrutinib should be administered per local prescribing guidelines (ie, Prescribing Information or Summary of Product Characteristics) and those guidelines should be followed throughout the study for these patients. The text below summarizes common current prescribing guidance, but local prescribing guidelines should always take precedence where applicable.

Ibrutinib will be administered at a dose of 420 mg orally once daily. Patients will take ibrutinib with water at approximately the same time every day. Ibrutinib, in any dosage form, should not be opened, broken, or chewed at any time. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with return to the normal schedule the following day. Extra doses of ibrutinib should not be taken to make up for the missed dose. If a patient vomits after taking ibrutinib, that dose should not be repeated.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any AE or SAE criterion must be reported in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for zanubrutinib or ibrutinib. 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 zanubrutinib, refer to [redacted] Additional information on the following precautions is detailed in this protocol:

- Surgery and procedures (see Section 6.4.1)
- Dose modifications for zanubrutinib when coadministered with CYP3A inhibitors and inducers (see Section 6.5.1.3)
- Tumor lysis syndrome (see Section 7.1.1)
- Infection prophylaxis (see Section 7.1.1)

For information on warnings and precautions for ibrutinib, refer to the most recent local prescribing information.

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.

Study treatment with ibrutinib should follow local prescribing information. Current prescribing guidelines state that ibrutinib should be held for 3 to 7 days pre and post-surgery, depending upon the type of surgery and the risk of bleeding.

6.5. Dose Interruption and Modification

The guidelines below should be followed for dose interruption or modification of zanubrutinib or ibrutinib in the event of toxicities. The dose reduction guidance refers to an individual toxicity event (ie, successive thrombocytopenia events) and is not cumulative amongst different events of the same class (ie, a thrombocytopenia event followed by a neutropenia event).

Assessment of the presence and severity of adverse events which may a trigger dose interruption and/or modification should follow the guidance in Section 8.1.

Management of toxicities via methods not involving the interruption and modification of study drug is discussed in Section 6.6.

If study drug is interrupted for > 28 days, written approval must be obtained from the medical monitor before study drug can be restarted (see Section 6.7).

For surgery and procedure guidance see Section 6.4.1.

6.5.1. Zanubrutinib

The guidelines below should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.5.1.1) and non-hematologic (Section 6.5.1.2) toxicities.

Table 2: Zanubrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Zanubrutinib dose (Arm A)
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
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

Zanubrutinib may be restarted upon resolution of toxicity or as otherwise specified per event. 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 medical monitor (Section 6.7).

6.5.1.1. Zanubrutinib Dose Reduction for Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment (using Hallek et al 2008) 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

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention should be discussed with the 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.

6.5.1.2. Zanubrutinib Dose Reduction for Non-hematologic Toxicity

Guidelines for non-hematologic toxicities are given in Table 3. For dose reductions, follow the guidance described in Table 2.

Table 3: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Re-start Dose
≥ 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.	Re-start at dose level (-1)
Any grade intracranial hemorrhage	Permanently discontinue zanubrutinib.	Not Applicable
Atrial fibrillation (AF) that is symptomatic and/or incompletely controlled	Hold until AF is clinically 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 either the original dose level or dose level (-1), at the discretion of the treating investigator

For subjects experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled, the study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator. Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.8.5.

6.5.1.3. Zanubrutinib Dose Modifications When taking CYP Inhibitors and Inducers

If strong/moderate CYP3A inhibitors and inducers are used during the trial (see Section 7.2.1) follow the dose modifications in Table 4. For use of prophylactic anti-infectives (ie,

voriconazole) during screening, it is recommended that patients stop the treatment at least 5 days before first dose of study treatment.

Table 4: Dose Modification 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)	Interrupt study drug; Consider alternative agents with less induction potential. If unavoidable, monitor for potential lack of efficacy.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	No dose modification necessary, use with caution.

A more comprehensive list of Strong/Moderate CYP3A Inhibitors and Inducers is found in Appendix 5

6.5.2. Ibrutinib

For dose modification of Ibrutinib, local prescribing guidelines appropriate for your country (ie, Prescribing Information or Summary of Product Characteristics) should be followed throughout the study. The information below uses one example of local prescribing guidelines, but local prescribing guidelines applicable to your country should always take precedence.

Table 5 below is an example of local prescribing information that describes the dose reduction levels for ibrutinib. Please follow your local prescribing info as applicable.

Table 5: Example of Local Prescribing Guidance for Ibrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Ibrutinib (Arm B)
First	0 = starting dose	Restart at 420 mg once daily
Second	-1 dose level	Restart at 280 mg once daily
Third	-2 dose level	Restart at 140 mg once daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

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 medical monitor (see Section 6.5).

Specific events may require dose reduction to specific doses outside the general dose reduction guidance in Table 5 (refer to Sections 6.5.2.2 and 6.5.2.3).

6.5.2.1. Ibrutinib Dose Reduction for Hematologic Toxicity

Local prescribing guidelines should be followed for dose reductions related to hematologic toxicity. An example of common local prescribing guidelines is given here, but follow the local prescribing guidelines applicable to your country.

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

- ≥ Grade 3 neutropenia with infection or fever
- Grade 4 hematologic toxicities.

Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib therapy may be re-initiated at the starting dose. If the toxicity recurs, reduce dose by 1 dose level (280 mg orally once daily). A second dose reduction to dose level -2 (140 mg orally once daily) may be considered as needed. If these toxicities persist or recur following 2 dose reductions, discontinue ibrutinib.

6.5.2.2. Ibrutinib Dose Reduction for Non-Hematologic Toxicity

Local prescribing guidelines should be followed for dose reductions related to non-hematologic toxicity. An example of common local prescribing guidelines is given here, but follow the local prescribing guidelines applicable to your country.

Ibrutinib should be interrupted for ≥ Grade 3 non-hematologic toxicities.

For patients with mild hepatic impairment, please follow local prescribing guidelines.

6.5.2.3. Ibrutinib Dose Modifications When Taking CYP Inhibitors and Inducers

Local prescribing guidelines should be followed for dose modifications related to CYP inhibitors and inducers. An example of common local prescribing guidelines is given here, but follow the local prescribing guidelines applicable to your country.

Table 6: Example of Local Prescribing Guidance for Dose Modifications for Use of Ibrutinib with CYP3A Inhibitors

Patient Population	Coadministered Drug	Recommended Ibrutinib Dose
B-Cell Malignancies	• Moderate CYP3A inhibitor • Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Interrupt dose as recommended (see Dosage and Administration Section 6.2)
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended (see Dosage and Administration Section 6.2)
	• Other Strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for 7 days or less), interrupt ibrutinib

6.6. Toxicity Management Recommendations

Additional recommendations are provided in Appendix 11 for the diagnosis and management of adverse events of interest (toxicity management). These recommendations are intended as guidance. Appendix 11 should be used in conjunction with expert clinical judgement (eg, by experts specializing in cardiology for management of atrial fibrillation), and individual institutional guidelines or policies.

6.7. Discontinuation from Study Treatment

Patients should discontinue study treatment for the following:

- Withdrawal from the study (see Section 5.13).
- Pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Intercurrent illness that compromises the patient's ability to participate in the study
- Unequivocal disease progression
  - Patients should remain on study treatment until disease progression is confirmed by independent central review.

  - Note that patients with disease progression may continue study drug treatment with zanubrutinib if they are benefiting from study treatment in the judgment of the investigators, with approval from the medical monitor.

- Need for prohibited medication
- Start of alternative anticancer therapy to treat the condition initially being evaluated in this study, or start of therapy for secondary malignancy that would interfere with assessment of zanubrutinib safety and efficacy
- Study drug interruption > 28 days (unless agreed by the investigator and the medical monitor)
- Significant, persistent, or recurrent AEs as described in Section 6.5

The investigator/patient may elect to discontinue study treatment for reasons other than those listed above, but are not required to do so. Withdrawal of consent to the study is not required to discontinue study treatment.

7. CONCOMITANT THERAPY

7.1. Concomitant Therapy

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

Patients with high tumor burden should be monitored closely, and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards for tumor lysis syndrome.

7.1.1. Permitted Medications

The following treatments are allowed:

- Blood product transfusion and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-CLL/SLL indications with the following restrictions:

  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). Chronic systemic corticosteroid use is not permitted, except for adrenal replacement.
- Therapy to reduce symptoms per standard of care and institutional guidelines

Tumor lysis syndrome has been infrequently reported with zanubrutinib and ibrutinib treatment. Patients with high tumor burden should be monitored closely, and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards.

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including *Pneumocystis jirovecii pneumonia* (PJP), prophylaxis should be considered as per institutional standards. Otherwise for other infection prophylaxis should be as per institutional standards.

7.1.2. Prohibited Medications

Patients should not receive other anticancer therapy (including but not restricted to chemotherapy, immunotherapy, corticosteroids for treatment of CLL, experimental therapy, radiotherapy, and herbal medications) during screening or while on treatment in this study. Other anticancer therapies should not be administered until disease progression (as per clinical practice standards at the study center), un-manageable toxicity, or no further clinical benefit occurs, which requires permanent discontinuation of the study drug.

7.2. Potential Interactions Between the Study Drugs and Concomitant Medications

7.2.1. CYP-Inhibiting/Inducing Drugs

7.2.1.1. Zanubrutinib

Zanubrutinib is primarily metabolized by CYP3A (Section 1.2.2.2). 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. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table in Table 4. The medical monitor should be consulted in these situations. Please refer to Appendix 5 and http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

A clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.2.2.2). 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). Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for $AUC_{0\text{-}t}$ and 34% for C_{max} (Section 1.2.2.2). 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.

7.2.1.2. Ibrutinib

Local prescribing guidelines should be followed for guidance on drug interactions and contraindications when using ibrutinib. An example of common local prescribing guidelines for use of ibrutinib with CYP3A Inhibitors is given in Table 6, Section 6.5.2.3, but follow the local prescribing guidelines applicable to your country.

Co-administration of strong or moderate CYP3A4 inhibitors (see Appendix 5 and Table 6, Section 6.5.2.3) with ibrutinib may lead to increased ibrutinib exposure and, consequently, a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased ibrutinib exposure and, consequently, a risk for lack of efficacy. Therefore, concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors/inducers should be avoided.

Do not take ibrutinib with grapefruit or Seville oranges (bitter oranges) - this includes eating them, drinking the juice, or taking a supplement that might contain them. This is because it can increase the amount of ibrutinib in the blood. Refer to Appendix 5 for examples of strong and moderate CYP3A inhibitors and CYP3A inducers.

Agents that may have their plasma concentrations altered by ibrutinib

Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor in vitro. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimize the potential for an interaction in the GI tract, oral narrow therapeutic range, P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP in the liver and increase the exposure of medicinal products that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

Based on in vitro data, ibrutinib is a weak reversible inhibitor towards CYP3A4 at the intestinal level and may therefore increase the exposure to CYP3A4 substrates sensitive to gut CYP3A metabolism. No clinical data are available on this interaction. Caution should be exercised if coadministering ibrutinib with CYP3A4 substrates administered orally with narrow therapeutic range (such as dihydroergotamine, ergotamine, fentanyl, cyclosporine, sirolimus and tacrolimus).

Based on in vitro data, ibrutinib is a weak CYP2B6 inducer and may have the potential to affect the expression of other enzymes and transporters regulated via the constitutive androstane receptor (CAR), eg, CYP2C9, CYP2C19, UGT1A1 and MRP2. The clinical relevance is not known, but the exposure to substrates of CYP2B6 (such as efavirenz and bupropion) and of co-regulated enzymes may be reduced upon co-administration with ibrutinib.

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 condition 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) related 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, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03. Patients with CLL may have low blood counts at initiation of therapy so assessment of AE severity for hematologic toxicity should be based on the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 9).

Toxicities that are not specified in the NCI-CTCAE will follow general NCI-CTCAE guidance as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or non-invasive 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.

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 transmission 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 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. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. 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 postmortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be re-sent to the sponsor within the time frames outlined in Section 8.6.1.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation) or other abnormal assessments (ECG, radiographical studies, and 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. Laboratory events indicating liver or renal dysfunction should be considered clinically significant.

For hematologic toxicities, refer to the Grading Scale for Hematologic Toxicity in CLL Studies (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 5.8.5.

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 was 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.
- Results in a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (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) 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.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drugs.

Beyond 30 days after the last dose of study drug the investigator should report any SAEs that are believed to be related to prior study drug treatment. SAEs that are not considered related to study treatment do not need to be reported and are not subject to the reporting requirements outlined in Section 8.6, but these SAEs should still be recorded in the EDC (see Section 11.2.6) per the guidelines outlined in Sections 8.1.1 and 8.2.

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?

8.5. Specific Instructions for Recording Adverse Events and Serious Adverse Events

8.5.1. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, 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). Adverse events secondary to disease progression should be clearly indicated as such. For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The AE term should be reported as "pleural effusion" instead of disease progression. If a patient experiences a fatal multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression".

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

8.5.2. Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death," "death of unknown cause," or "death unexplained."

8.6. Prompt Reporting of Serious Adverse Events

8.6.1. Time Frames for Submitting Serious Adverse Events

SAEs will be reported promptly (within 24 hours of first knowledge of the SAE) to the sponsor or designee as described once the investigator determines that the AE meets the protocol definition of an SAE.

Table 7: Time Frames and Documentation for Reporting SAEs to the Sponsor or Designee

	Time frame for making initial report	Documentation method	Time frame 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

Abbreviation: SAE, serious adverse event.

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 within 24 hours. The SAE report will always be completed as thoroughly as possible with all available details of the SAE 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 study contacts for SAE receipt.

8.6.2. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.1 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 toward 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)/IEC.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

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.

8.7. 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 study drug, 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 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 AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an 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 an SAE.

8.8. 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.

8.9. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent 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 SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- [redacted]
- Ibrutinib Prescribing Information

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the sponsor or designee. Data will be listed and summarized according to sponsor -agreed reporting standards.

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 ORR (PR or higher, defined as CR/CRi + PR + nodular PR) determined by investigator assessment using the "modified" 2008 IWCLL guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL (Appendix 2) and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL (Appendix 3). While the primary efficacy endpoint is per investigator assessment, ORR per independent central review will also be analyzed to support the primary analysis. [redacted]

9.1.2. Secondary Endpoints

Key Secondary Endpoint:

The key secondary endpoint is PFS, defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, determined by the investigator. While the key secondary efficacy endpoint is per investigator assessment, PFS per independent central review will also be analyzed to support the key secondary endpoint analysis. [redacted]

Other Secondary Endpoints:

- Duration of response, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first, determined by independent central review
- Duration of response by investigator assessment
- Time to treatment failure, defined as time from randomization to discontinuation of study drug due to any reason
- Rate of PR-L or higher, defined as the proportion of patients who achieve a CR/CRi + PR + nodular PR + PR-L determined by independent central review
- Overall survival, defined as the time from randomization to the date of death due to any cause
- PROs measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs

[redacted]

9.2. Statistical Analysis

9.2.1. Randomization Methods

Patients will be randomized using the Interactive Response Technology system for this study by permuted block stratified randomization.

The stratified randomization using age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present versus absent) as stratification factors will be produced, reviewed, and approved by an independent statistician.

9.2.2. Analysis Sets

The Intent-to-Treat Analysis Set includes all randomized patients. The Intent-to-Treat Analysis Set will be the primary analysis set for 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 drug and had no major protocol deviations. Criteria for exclusion from the Per-protocol Analysis Set will be determined and documented before the database lock for the primary analysis. For the primary analysis of non-inferiority testing in ORR, the Per-protocol Analysis Set will be used as the secondary population.

[redacted]

9.2.3. Subject Disposition

The number of patients screened, randomized, randomized but not treated, treated, discontinued from study drug, and discontinued from study will be summarized. The primary reason for study drug discontinuation and study discontinuation will be summarized according to the categories recorded in the eCRF.

9.2.4. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized in the Intent-to-Treat Analysis Set using descriptive statistics. Continuous variables include age, weight, vital signs, and time since initial CLL/SLL diagnosis; categorical variables include sex, age group, race,

disease stage, ECOG-performance status, geographic region, and genetic status including del17p, del11q, 12q+, and IGHV mutation analysis.

9.2.5. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report for this protocol. Prior medications will be defined as medications that started before the first dose of study drug, whether continuing at or stopped at the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

9.2.6. Efficacy Analysis

9.2.6.1. Primary Efficacy Endpoint Analyses

The primary hypothesis testing for the primary endpoint of ORR [redacted] will be to demonstrate the non-inferiority of zanubrutinib to ibrutinib. The null and alternative hypotheses for the non-inferiority test are as follows:

- H_{0NI}: Response Ratio (zanubrutinib/ibrutinib) ≤ 0.8558
- H_{aNI}: Response Ratio (zanubrutinib/ibrutinib) > 0.8558

One interim analysis will occur approximately 12 months after 415 patients (69% information fraction) have been randomized. The final analysis will occur approximately 12 months after 600 patients have been randomized.

A Cochran-Mantel-Haenszel test for response ratio adjusting for the 4 randomization stratification factors (age [< 65 years versus ≥ 65 years], geographic region (China versus non-China), refractory status [yes or no], and del17p/TP53 status [present versus absent]) will be performed for the hypothesis testing. The p-value from the test will be compared against the monitoring boundaries for the non-inferiority testing (Table 8) and used for the primary inference. The treatment effect in ORR and its 95% Wald confidence interval (CI) will be estimated, and the Clopper-Pearson 95% CIs will be calculated for ORR for each treatment group.

If the non-inferiority is demonstrated either at the interim or the final analysis, further testing for the superiority of zanubrutinib to ibrutinib will be performed (Brannath et al 2003). The null and alternative hypotheses for the superiority test are as follows:

- $H_{0\ SUP}$: Response Ratio (zanubrutinib/ibrutinib) ≤ 1
- $H_{a\ SUP}$: Response Ratio (zanubrutinib/ibrutinib) > 1

The monitoring boundaries for the non-inferiority and superiority tests are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function and are listed in Table 8 and Table 9. The monitoring boundaries will be adjusted based on the actual information

fraction (number of subjects for ORR) observed up to the data cutoff. Deviation from the scheduled interim analysis will not affect the overall type I error (Lan and DeMets 1983).

Table 8: Monitoring Boundaries for the ORR Non-inferiority Testing

	Number of patients evaluable	Information fraction	Nominal p-value boundary (primary inference)	Response ratio boundary
Interim	415	69%	0.007	1.003
Final	600	100%	0.023	0.956

Abbreviation: ORR, overall response rate.

Table 9: Monitoring Boundaries for the ORR Superiority Testing

	Number of patients evaluable	Information fraction	Nominal p-value boundary (primary inference)	Response ratio boundary
Interim	415	69%	0.007	1.167
Final	600	100%	0.023	1.11

Abbreviation: ORR, overall response rate.

Justification of the Non-inferiority Margin

A non-inferiority margin of 0.8558 in response ratio was derived using the 95% to 95% fixed margin approach (FDA Guidance for Industry Non-Inferiority 2016). In the RESONATE trial (Byrd et al 2014), the ibrutinib effect over ofatumumab represented by the ratio of response rate (PR or higher) was 10.43 with a 95% CI of (5.2, 21.0) based on the independent review committee assessment. In the RESONATE2 trial (Burger et al 2015), the ibrutinib effect over chlorambucil represented by the ratio of response rate (PR or higher) was 2.33 with a 95% CI of (1.83, 2.97) based on the independent review committee assessment. In a fixed-effect meta-analysis of the 2 studies using inverse variance weighting, the ibrutinib effect in response rate ratio is estimated as 2.7392 with a 95% CI of (2.1781, 3.4450). Thus, M1 is 2.1781, the lower bound of the 95% CI. Since the effect sizes of ibrutinib are overactive controls in both studies (ofatumumab and chlorambucil, respectively), rather than placebos, the choice of M1 is very conservative and results in a narrow margin. Requiring 80% of M1 to be retained (on the log scale) in zanubrutinib to demonstrate non-inferiority generates a non-inferiority margin of 0.8558 (for the response ratio), which is within the clinically acceptable limit.

9.2.6.2. Secondary Efficacy Endpoint Analyses

If the primary objective of demonstrating the non-inferiority of zanubrutinib to ibrutinib in ORR is met, the treatment effect of the key secondary efficacy endpoint of PFS by investigator assessment (for the United States, by independent central review) will be tested for non-inferiority under hierarchical testing to control the study-wise type I error.

If non-inferiority is demonstrated for the key secondary efficacy endpoint of PFS, further testing of superiority will be performed for the endpoint (Brannath et al 2003).

Treatment arm comparison for the other secondary efficacy endpoints will be descriptive, and no hypothesis testing will be performed.

Key Secondary Efficacy Endpoints

Progression-free Survival

The non-inferiority of zanubrutinib to ibrutinib for PFS will be tested under the non-inferiority margin of 1.3319 (for the hazard ration [HR] of zanubrutinib/ibrutinib) using a stratified log-rank test based on the 4 randomization stratification factors: age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present versus absent). The null and alternative hypotheses to test the non-inferiority are as below:

- H_{0NI}: HR (zanubrutinib/ibrutinib) ≥ 1.3319
- H_{aNI}: HR (zanubrutinib/ibrutinib) < 1.3319

There will be a single analysis of PFS for the purpose of inference when approximately 205 PFS events have occurred; however, a one-sided significance level of 0.00001 will be applied to the analysis of PFS at the time when ORR is analyzed to compensate for the potential type I error increase from the descriptive analysis. Two hundred five (205) PFS events are expected to accrue [redacted] months after study start (as described in Section 9.4). If the p-value from the stratified log-rank test for non-inferiority is significant, the non-inferiority of zanubrutinib to ibrutinib in terms of PFS will be demonstrated. Further testing of superiority in terms of PFS will be performed in this case.

The non-inferiority margin of 1.3319 was derived using the 95%-95% fixed margin method based on a meta-analysis of the RESONATE and RESONATE 2 studies. In the RESONATE2 study, the estimated PFS HR for ibrutinib versus chlorambucil is 0.16 with a 95% CI of (0.09, 0.28). In the updated RESONATE results (Brown et al 2014), the estimated PFS HR for ibrutinib versus ofatumumab is 0.106 with a 95% CI of (0.073, 0.153). In a fixed-effect meta-analysis, the pooled HR is estimated as 0.120 with a 95% CI of (0.088, 0.163). Therefore, the control arm effect (M1) is -0.163 in HR and 1.814 in log HR. Requiring 84.2% of M1 to be retained in zanubrutinib, a non-inferiority margin of 1.3319 for the HR (zanubrutinib/ibrutinib) is generated.

The HR for PFS and its 95% CI will be estimated from a stratified Cox regression model.

The distribution of PFS including median and other quartiles, and PFS rate at selected timepoints, will be estimated using the Kaplan-Meier method for each arm.

PFS will be calculated as the time from the date of the randomization to the date of the first documentation of disease progression or death due to any cause, regardless of the use of subsequent anticancer therapy prior to the documented PD or death. PFS for the patients without a documented PD or death will be censored at the last disease assessment.

Other Secondary Efficacy Endpoints

Duration of Response

The distribution of DOR by independent central review including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group. There will be no

treatment arm comparison for DOR. The same analysis will be performed for DOR by investigator assessment. The same censoring rule used in the PFS analysis will be used for the analysis of DOR.

Time to Treatment Failure

The HR for time to treatment failure and its 95% CI will be estimated from a stratified Cox regression using the 4 randomization stratification factors (age [< 65 years versus ≥ 65 years], geographic region (China versus non-China), refractory status [yes or no], and del17p/TP53 status [present versus absent]). The Kaplan-Meier method will be used to estimate the distribution of time to treatment failure for each treatment group.

Time to treatment failure will be calculated as the time from the date of randomization to the date of discontinuation of study treatment due to any cause. Time to treatment failure will be censored at the data cutoff for the patients who did not discontinue study treatment.

Rate of PR-L or Higher by Independent Central Review

Rate of response ratio for PR-L or higher by independent central review and its 95% Wald CI will be estimated using the Cochran-Mantel-Haenszel method. Clopper-Pearson 95% CI for the rate of response will be calculated for each treatment group.

Overall Survival

OS will be analyzed using the same methods employed for PFS by investigator assessment.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint for each treatment group. 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 2 treatment groups. The data may also be analyzed using repeated measure mixed model to account for missing data under the Missing at Random assumption.

Changes in the EQ-5D-5L will be summarized for each treatment group.

[redacted]

9.2.6.4. Sensitivity Analyses

For PFS, alternative censoring rules such as censoring for new anticancer therapy will be used as sensitivity analyses. Details of sensitivity analyses will be described in the SAP.

[redacted]

9.3. Safety Analyses

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v4.03. Laboratory values (CBC, serum chemistry, and coagulation), vital signs, physical exams, and ECG findings will also be used in the safety assessment. Descriptive statistics will be used to analyze all safety data by the actual treatment group.

9.3.1. Extent of Exposure

The extent of exposure to the 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, 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 category.

Patient data listings will be provided for all dosing records.

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) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class will also be captured in the database.

A treatment-emergent AE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days following the study drug discontinuation or the start of a new anticancer therapy, whichever comes first. After this period, only treatment-related SAEs are to be reported (per Section 8.4.1). Only the AEs that are treatment-emergent will be included in the summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of treatment-emergent AEs will be reported as the number (and percentage) of patients with treatment-emergent 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 treatment-emergent AEs within a specific system organ class and preferred term. The number (percentage) of patients with treatment-emergent AEs will also be summarized by the relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to

the study drug or with a missing assessment of the causal relationship. SAEs, deaths, treatment-emergent AEs ≥ Grade 3, study drug-related treatment-emergent 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

Selected CBC components 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 of (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for the laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by the 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, phosphorus, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for the vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, and weight) and the 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 as described in Section 5.5.4 and in Appendix 10. Descriptive statistics for absolute and change from baseline ECG parameters will be presented.

9.4. Sample Size Consideration

The sample size calculation is based on the primary efficacy analysis for the primary endpoint of ORR. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.03 (72%/70%), 600 patients will provide more than 90% power to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio) and 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction. The response rate for ibrutinib is approximated from published clinical data (Byrd et al 2019).

Assuming an HR (zanubrutinib arm/ibrutinib arm) of 0.9, 205 events are required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 1.3319 (HR) in PFS

[redacted]

[redacted] A median PFS of [redacted] months for ibrutinib and an exponential distribution for PFS are also assumed.

9.5. Interim Analysis

There will be 1 interim analysis for the non-inferiority (and the superiority if the non-inferiority is met) testing of ORR. The interim analysis will be performed approximately 12 months after the randomization of 415 patients. The monitoring boundaries for the interim and the final analyses for the non-inferiority and superiority tests are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function and are depicted in Table 8 and Table 9 (Section 9.2.6.1).

If the boundary is met for the interim non-inferiority analysis and the DMC recommends stopping the study, the sponsor may stop the study and file the results to the regulatory agencies for approval.

9.6. Final Analysis

If the primary objective of the ORR non-inferiority is met, the study will continue to follow up for PFS until 205 events are observed, which is estimated to be approximately [redacted] months from study start.

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 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 and also perform the interim efficacy analysis. 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 this study. This will be conducted by qualified, board-certified radiologists and hematologists assigned to this study. 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 Clinical Study Report 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 of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results would 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 an 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 Council on Harmonisation guidelines and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations 312, Subpart D, "Responsibilities of sponsors and Investigators," 21 Code of Federal Regulations, Part 50, and 21 Code of Federal Regulations, Part 56, are adhered to.

11.2.2. Ethical Conduct of the Study and Ethics Approval

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

The sponsor's sample ICF will be provided to each investigator who shall adapt it, subject to sponsor's approval, for use at his/her site. The investigator (or sponsor, where applicable) is responsible for ensuring that: 1) this protocol, 2) the study center's ICF, and 3) any other information or forms that will be presented to potential patients (eg, advertisements, Health Insurance Portability and Accountability Act of 1996 authorization, 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 ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

11.2.2.1. Protocol Amendments

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted by the investigator (or sponsor, where applicable) 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 - 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.

If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator (or sponsor, where applicable) 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 ICF 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 ICF/other information and the approved amended ICF/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 ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent must 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.

In the event that the ICF or other form signed by the patient is amended during their participation in the study, patients must be re-consented to the most current version of the ICFs or form. For any updated or revised ICFs or forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was reobtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site master study file and must be available for verification by study monitors at any time.

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.6.2, 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

The investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

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 ICF process, either as part of the ICF or as a separate signed document (for example, in the United States, a site-specific Health Insurance Portability and Accountability Act of 1996 consent may be used).

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location. Only patient initials (where allowed), date of independent central review, and an identification code (ie, not names) should 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 Investigator's Brochure, this protocol, eCRFs, 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.

If the written contract for the conduct of the study includes confidentiality provisions regarding BeiGene's confidential information inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

11.2.6. Data Collection

Data required by the protocol will be entered into an EDC system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Statement of Investigator Form must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

11.2.7. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the course of the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

AEs will be coded using the MedDRA Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.0 or higher.

11.2.8. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or sharing such outputs from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the trial is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

11.2.9. Drug Accountability at Site

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 where applicable (quantity and condition), patient-drug dispensation records, and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and/or commercially sourced, quantities dispensed to patients, and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, sites should have an appropriate standard operating procedure for study drug disposal/destruction. 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 and applicable law, including that regarding disposal of hazardous waste. 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.

11.2.10. Inspections, Audits, and Monitoring Visits

The investigator must ensure the facilities used for this trial and all the 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.

11.2.11. 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.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and, if applicable, to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

11.2.12. 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 interest of clinical investigators and/or disclose those financial interests, as required by 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. Study Report and Publications

A Clinical Study Report 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 trial 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 prior to submission or presentation in accordance with the clinical study agreement. 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. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

11.4. 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
- [redacted]

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 with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. 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 still be provided 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.

11.5. 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, eCRF 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 eCRFs) 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 or responsibility for 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 the shorter of: a period of up to 10 years or as allowed by the IRB/IEC. A longer storage period may apply in the event that subjects consent to BeiGene retaining remaining samples for future research (Section 5.15).

11.6. 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) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights, whether or not patentable, 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 in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 11.3.

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.

11.7. Joint Investigator/Sponsor Responsibilities

11.7.1. 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 in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs 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 eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected or queries raised in the course of these monitoring visits are resolved.

11.7.2. 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 cooperate with representatives of a regulatory agency and BeiGene and to provide them access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. REFERENCES

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Zydelig® - Summary of Product Characteristics: 15 December 2016.

APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

PROTOCOL NO: BGB-3111-305; Amendment 3.0

This protocol is a confidential communication of BeiGene, Ltd. and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. 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. or one of its subsidiaries.

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[c]	Partial Response[e]	Partial Response with Lymphocytosis[g]	Progressive Disease[h]
Group A				
Lymphadenopathy[a]	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	
Marrow[b]	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi[d]	50% reduction in marrow infiltrate, or B-lymphoid nodules[f]	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils[b]	> 1500/µL	> 1,500/µL or > 50% improvement over baseline	> 1,500/µL or > 50% improvement over baseline	

Abbreviations: CLL, chronic lymphocytic leukemia; CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PD, progressive disease; PR, partial response.

Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

a. Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination).
b. These parameters are irrelevant for some response categories.
c. Complete response: all the criteria have to be met, and patients have to lack disease-related constitutional symptoms.
d. Complete response with incomplete marrow recovery: all the criteria met for complete response except for hypocellular bone marrow.

e. Partial response: at least 2 of the criteria of group A plus 1 of the criteria of Group B must be met. *If only one Group A parameter is abnormal at baseline, then one Group A parameter is sufficient. Bone marrow results are not required as a Group A parameter to determine PR unless that is the only Group A parameter abnormal at baseline.*
f. Nodular partial response: all the criteria met for complete response except for the presence of lymphoid nodules in the bone marrow
g. Partial response with lymphocytosis: blood lymphocytes decreased < 50% or increased from baseline + otherwise meeting criteria for PR
h. Progressive disease: at least 1 of the above progressive disease criteria must be met.

- Stable disease: is absence of progressive disease and failure to achieve at least a PR-L

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 may not be 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 may not be a sign of treatment failure or progressive disease. Isolated increase in lymph nodes and/or splenomegaly during periods of study drug hold may occur leading to PD. Sites should do their best to obtain CT scans and perform response assessments using the time allotted in assessment windows to avoid this situation. Patient may continue study treatment post first assessed PD if it is perceived that the patient will benefit from continued treatment. After the second assessment of PD, the patient must discontinue from study treatment. In rare instances, after discussion with the Medical Monitor, the patient may remain on study treatment even after the second assessment of PD.

APPENDIX 3. THE LUGANO CLASSIFICATION FOR CT-BASED RESPONSE FOR SLL (CHESON ET AL 2014)

Response and Site	CT-Based Response
Complete	
Lymph nodes and extralymphatic sites	Complete radiologic response (all of the following): • 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, IHC negative
Partial	
Lymph nodes and extralymphatic sites	Partial remission (all of the following): • ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extranodal sites and no criteria for PD are met • 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	
Target nodes/nodal masses, extra-nodal lesions	Stable disease < 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

Response and Site	CT-Based Response
Bone marrow	Not applicable
Progressive disease*	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 • 0.5 cm for lesions ≤ 2 cm • 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
Individual target nodes/nodal masses	
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

Source: Cheson et al 2014.
Abbreviations: CT, computed tomography; IHC, immunohistochemistry; PD, progressive disease.

Modification from Lugano Classification for NHL (Cheson et al 2014)**:**

*Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days 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 during periods of study drug hold may occur leading to PD. Sites should do their best to obtain CT scans and perform response assessments using the time allotted in assessment windows to avoid this situation. Patients may continue study treatment post-first assessed PD if it is perceived that the patient will benefit from continued treatment. After the second assessment of PD, the patient must discontinue from study treatment. In rare instances, after discussion with the Medical Monitor, the patient may remain on study treatment even after the second assessment of PD.
**Splenomegaly defined as vertical spleen length > 13 cm.

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

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Food products: grapefruit juice [a]
Other: cobicistat, conivaptan, elvitegravir, nefazodone, diltiazem, idelalisib
Protease inhibitors: nelfinavir, ritonavir or ritonavir[b] in combination with danoprevir/elvitegravir/indinavir/lopinavir/paitprevir and (obitasvir and/or dasabuvir)/saquinavir/tipranavir
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Calcium channel blockers: verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Others: aprepitant, cimetidine, cyclosporine, dronedarone, tofisopam, fluvoxamine
Strong CYP3A Inducers
Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Moderate CYP3A Inducers
Bosentan, efavirenz, etravirine, modafinil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (9/26/2016).
Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.
Note: 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.

a. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg,, low dose, single strength).
b. Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

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 ❑

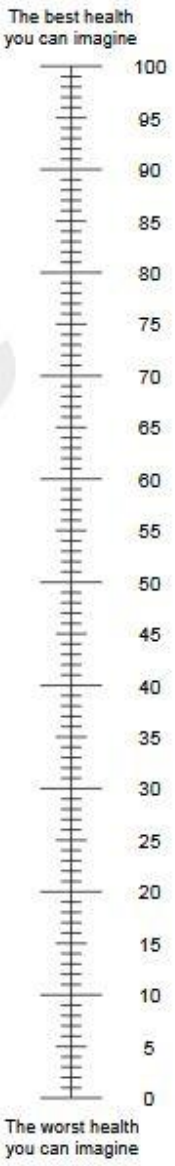
ANXIETY / DEPRESSION

- 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 = ☐



3

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%	≥ 2,000
1	11%-24%	≥ 1,500 and < 2,000
2	25%-49%	≥ 1,000 and < 1,500
3	50%-74%	≥ 500 and < 1,000
4	≥ 75%	< 500

Source: Hallek et al 2008.
Abbreviation: ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia
Hgb: hemoglobin; WBC, white blood cell;

[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 (1,000/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 (1,000/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

	Screening	Enrollment/ Randomization[a]	Treatment Period (1 cycle = 28 days)					End of Treatment (Section 6.7)	Post-Treatment Follow-Up		
Cycle	–		**1**	**2 to 3**	**4**	**5 to 6**	**Every 3 Cycles beginning Cycle 7 (C7, 10, etc.)**		**End of Treatment[b]**	**Long-term Follow-up[c]**	**Survival Follow-up[d]**
Cycle Day	**-35 to randomization**	**-5 to -1 prior to C1D1**	**1[e]**	**1**	**1**	**1**	**1**		**30 days after EOT**	**Every 24 weeks**	
Window (Days)	–		**-**	**± 2**	**± 2**	**± 2**	**± 6[f]**		**+ 7 days**	**± 14 days**	
Informed consent, screen number[g]	X										
Medical & cancer history	X										
Eligibility authorization packet[h]	X										
Randomization/Treatment arm assignment[i]	X										
Zanubrutinib & ibrutinib dispensing/accountability[j]			X	X	X	X	X[j]				
Safety Assessments								Continue Until			
Cardiac function	X										
Vital signs (temperature, BP, heart rate)	X		X	X	X	X	X		X		
Physical examination[l]	X		X	X	X	X	X		X		
ECOG performance status	X		X	X	X	X	X		X		
12-Lead ECG (local read)[m]	X		X	X	X		X				
Concomitant medications review	X		X	X	X	X	X		X		
AE review[n]	X	X	X	X	X	X	X		X	X[n]	
Survival status of patient											X

Efficacy Assessments											
Overall response assessment					X		X[o]		X	X	
Disease-related constitutional symptoms	X				X		X		X	X	
Physical exam of liver, spleen & lymph nodes	X				X		X		X	X	
CT with contrast[p]	X				X		X[o]		X[q]	X	
Bone marrow examination[r]	X		As needed[r]						As needed	X	
PRO Questionnaires[s]											
EQ-5D-5L			X		X		X		X	X	
EORTC QLQ-C30			X		X		X		X	X	
[redacted]	[redacted]										
Laboratory Assessments											
Hematology[u], chemistry[v]	X[w]		X	X	X	X	X		X	X	
Serum immunoglobulins	X				X		C7 then every 6 cycles				
Coagulation	X										
Hepatitis B & C testing[x]	X										
HIV testing [y]	X										
Pregnancy test (if applicable)[z]	X		X	X	X	X	Every cycle		X		
Biomarker Assessments											
del17p by FISH[aa]	X										
Molecular analyses[bb]	X	X[bb]							X[bb]		
HBV DNA screening by PCR[cc]			Every cycle								
Flow Cytometry[dd]	X	X									

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; BTK, Bruton tyrosine kinase; C#, Cycle #; CR, complete response; CRi, complete response with incomplete bone marrow recovery; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IEC, Independent Ethics Committee; IGHV, immunoglobulin variable region heavy chain; INR, international normalized ratio; MRI, magnetic resonance imaging; [redacted]; PD, progressive disease; [redacted] PRO, patient-reported outcome; SAE, serious adverse event.

a. Time between randomization and Day 1 should be no more than 5 days. See Section 5.2.5.

b. Approximately 30 days (+ 7 days) after permanent treatment discontinuation or before initiation of a new anticancer therapy, whichever comes first. See Section 5.12.1.
c. Visits repeat every 24 weeks (± 14 days) after End of Treatment. Assessments during this phase are conducted primarily to assess disease progression. See Section 5.12.2.
d. Survival Follow-up phase is for patients who have ended treatment and progressed. A study visit is not mandatory during Survival-Follow-up: see Section 5.12.3.
e. All Day 1 assessments should occur pre-dose unless otherwise specified.
f. Cycle 7 has a ± 2 day window
g. Informed consent and assignment of screen number must occur before any study specific procedures, and may be obtained before the screening window begins. Consent must be obtained on the current version of the form approved by the IEC. See Section 5.2.
h. 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 the medical monitor or designee will provide final approval for enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with Day 1 study procedures. See Section 5.2.4.
i. Patients will be randomized 1:1 to one of two arms - Arm A: zanubrutinib or Arm B: ibrutinib. See Section 3.1 and Section 9.2.1.
j. Zanubrutinib will be administered 160 mg orally twice daily with or without food (See Section 6.2.1). Ibrutinib will be administered 420 mg orally once daily (See Section 6.2.2). Study drug (both zanubrutinib and ibrutinib) may be supplied and dispensed as frequently as every cycle and accountability should be done at that time (See Section 6.1.4). Please refer to the pharmacy manual for further information and the most recent guidance on study drug supply frequency during the trial.
k. [redacted]
l. Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at Screening only). Assessment of vital signs and a focused physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days. See Section 5.5.2.
m. Perform a 12-lead ECG in triplicate at screening for all subjects. For subjects assigned to the zanubrutinib arm, one 12-lead ECG will be performed at, pre-dose (within 30 min prior to dose) and 2 hours (± 30 min) post-dose on Day 1 of Cycles 1 and 2, and one 12-lead ECG performed on Day 1 of Cycles 3 and 4 and Day 1 of every 3 cycles thereafter (at Cycle 7, Cycle 10, etc) until EOT. The ECG can be performed at either pre-dose or post-dose. For subjects assigned to the ibrutinib arm, a 12-lead ECG in triplicate will be performed at Day 1 of Cycles 1, 2, 3, and 4 and Day 1 of every 3 cycles thereafter (Cycle 7, Cycle 10, etc) until EOT. The ECG can be performed at either pre-dose or post-dose. See Section 5.5.4.
n. 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 30 days after the last dose of study drug. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. In addition, arrhythmia signs/symptoms will be reviewed at every visit. This will involve the investigators asking subjects for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness or fainting), as part of the routine AE monitoring for each visit. See Section 8.4.1.
o. Efficacy will be assessed every 6 cycles following C25 (C31, C37, C43, etc.) until progression. Patients that end treatment but do not progress will continue to conduct efficacy assessments as part of Long-term Follow-up (See Section 5.12.2).
p. CT with contrast of neck, chest, abdomen, and pelvis to be performed at Screening, Cycle 4 Day 1, then every 3 cycles until Cycle 25, followed by every 6 cycles thereafter, until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Copies of all scans will be sent for independent central review for response assessment. MRI may be used in place of CT; for details on imaging requirements see Section 5.6.3. All imaging should use the specified visit window or a ± 7-day window, whichever is longer. Imaging is to be performed as scheduled, independent of study drug hold.

q. Imaging does not need to be repeated if performed within 45 days before the End of Treatment Visit.
r. Bone marrow biopsy and aspirate are required during 1) the screening period. Fifteen unstained slides or archival block of a previously performed diagnostic bone marrow biopsy are acceptable if within 90 days of randomization. Aspirate only required for patients with SLL; 2) if clinical and laboratory results demonstrate a potential CR or CRi. This should be done within 40 days from the CT/MRI meeting the criteria of CR/CRi. If this is done and patients show bone marrow involvement preventing CR/CRi classification it should recheck bone marrow at least once every 12 months until CR or CRi is confirmed as long as the patient is still showing evidence of CR or CRi outside of bone marrow results. Recheck may be done earlier than 12 months as clinically indicated. [redacted]
s. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug, and before performing any other procedures. See Section 5.7.

[redacted]

u. Complete blood count and differential will be evaluated by a central or local laboratory. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil). See Section 5.8.1.
v. Serum chemistry will be evaluated by a central or local laboratory. Serum chemistry includes sodium, potassium, chloride, bicarbonate (carbon dioxide, or if neither is available carbon dioxide combining power), glucose, blood urea nitrogen (or serum urea), creatinine, calcium, phosphate (or phosphorus), magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. See Section 5.8.2.
w. The following 2 chemistry tests will only be done at Screening: direct antiglobulin test and β-2 microglobulin. See Section 5.8.2.
x. Hepatitis B serology includes HBsAg, HBcAb, HBsAb. Patients who are HBcAb positive, HBsAg negative, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) as outlined in Section 5.8.5. Hepatitis C serology includes HCV antibody. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) every cycle. Viral hepatitis B and C testing will be performed in a central laboratory, but may be performed locally if local testing sensitivity is adequate and after discussion with the medical monitor. See Section 5.8.5.
y. HIV test will be performed locally. HIV testing will be performed during Screening unless previous HIV test results from ≤ 4 weeks prior to Screening are available. See Section 5.8.7.
z. 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. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Day 1 of every cycle and for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. See Section 5.8.6.
aa. Blood samples (heparin) will be collected at the time of screening to assess prognostic factors such as del17p by FISH in a central laboratory (see the Laboratory Manual for details)
bb. Blood samples (EDTA) are required at the time of Screening, [redacted] for the assessment of mutations by molecular methods in a central laboratory (see the Laboratory Manual for details). See Section 5.9.
cc. Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo at least once on every cycle HBV DNA monitoring by PCR. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every 90 days (every third cycle). See Section 5.8.5.
dd. [redacted]

APPENDIX 11. SELECT ADVERSE EVENTS OF INTEREST: TOXICITY MANAGEMENT

The recommendations below for the diagnosis and management of adverse events of interest are intended as a guidance. This Appendix should be used in conjunction with expert clinical judgement (eg, by experts specializing in cardiology for management of atrial fibrillation), and individual institutional guidelines or policies. Local prescribing guidance for ibrutinib applicable to your country should always take precedence for your country as applicable.

<table>
<tr><th>Toxicity</th><th>Grade (per CTCAE 4.03 or Hallek et al, 2008)</th><th>Treatment Guidelines (Subject to Clinical Judgement)</th><th>Study Drug Management</th></tr>
<tr><td rowspan="4">Atrial Fibrillation</td><td>1
Asymptomatic, intervention not indicated</td><td rowspan="3">For all grades, recommend consultation with cardiologist for co-management of patients on study and to help determine the overall risk of embolic stroke versus bleeding. The usage of the CHA2DS2-VASc risk assessment tool can be helpful. When selecting medical therapy for these patients, consider avoiding strong CYP3A4 inducers and inhibitors (Section 7.2.1).
If the patient requires anticoagulation, recommend minimizing other medications associated with increased bleeding risk; however, decisions needed to be balanced by the need for such medications in consultation with other specialists. Warfarin is highly discouraged given known bleeding risk.</td><td rowspan="2">Recommend continuation of study treatment especially if CHA2DS2-VASc score is 0 or 1 and no anticoagulation is indicated.</td></tr>
<tr><td>2
Non-urgent medical intervention indicated</td></tr>
<tr><td>3
Symptomatic and incompletely controlled medically</td><td rowspan="2">For atrial fibrillation/flutter ≥ Grade 3, follow the dose reductions described in Section 6.5.1 for zanubrutinib and Section 6.5.2 for ibrutinib. For subjects experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: After the atrial fibrillation is adequately controlled, the study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator.
Patients who have intracranial hemorrhage in the context of atrial fibrillation should permanently discontinue treatment.</td></tr>
<tr><td>4
Life-threatening consequences; urgent intervention indicated</td><td>If patients are unstable, urgent referral to a cardiologist and evaluation for cardioversion and/or therapeutic anticoagulation is recommended.</td></tr>
</table>

Toxicity	Grade (per CTCAE 4.03 or Hallek et al, 2008)	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Anemia[a] (per Hallek et al 2008)	**1** 11%-24% decrease from pretreatment value	Follow institutional guidelines if any intervention is needed.	Recommend continuation of study treatment. If severe bleeding is also identified, study drug should then be held, until bleeding has resolved.
	2 25%-49% decrease from pretreatment value		
	3 50%-74% decrease from pretreatment value	Consider workup for possible sources of bleeding. Consider possibility of autoimmune hemolytic anemia. Follow institutional guidelines regarding transfusion of red blood cells. If anemia persists or recurs, consider more extensive workup, including possible bone marrow examination.	
	4 ≥75% decrease in pretreatment value		For ibrutinib, hold study treatment; resume when resolved/improved to ≤ Grade 1. Follow the dose reductions described in Section 6.5.2. For zanubrutinib, if anemia is considered unrelated to study drug, continue study treatment, unless severe bleeding is also identified. Otherwise, follow the dose reductions described in Section 6.5.1.
Neutropenia	**1** 1500-2000/mm^3; 1.5–2.0 x 10^9/L	If neutropenia is associated with fever or suspected infection, consider hospitalization and treatment with antibiotics per local standard of care.	Recommend continuation of study treatment.
	2 1000–1500 mm^3; 1.5–2.0 x 10^9/L		
	3 500-1000/mm^3; 0.5-1.0 x 10^9/L	If neutropenia is associated with fever or suspected infection, consider hospitalization and treatment with antibiotics or granulocyte stimulating cytokines such as G-CSF per local standard of care. Persistent or recurrent neutropenia should lead to further workup, including possible bone marrow examination.	For ibrutinib, hold study treatment if neutropenia is associated with fever or suspected infection. Resume when resolved/improved to ≤ grade 1. Follow the dose reductions described in Section 6.5.2. For zanubrutinib, dosing will be held for individual patients
	4 <500/mm^3; <0.5 x 10^9/L		

Toxicity	Grade (per CTCAE 4.03 or Hallek et al, 2008)	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
			under any of the following conditions, based on investigator assessment of study drug relatedness: Grade 4 neutropenia (lasting > 10 days) ≥ Grade 3 febrile neutropenia Follow the dose reductions described in Section 6.5.1.
Thrombocytopenia	**1** 11%-24% decrease from pretreatment value	Intervention per institutional guidelines. Monitor closely for bleeding events.	Recommend continuation of study treatment. If severe bleeding is also identified, study drug should then be held until bleeding has resolved.
	2 25%-49% decrease from pretreatment value		
	3 50%-74% decrease from pretreatment value		Continue ibrutinib unless severe bleeding is also identified. Otherwise, follow dose reductions described in Section 6.5.2. Hold zanubrutinib if any grade 3 thrombocytopenia associated with significant bleed requiring medical intervention. Discuss with medical monitor. Otherwise, follow the dose reductions described in Section 6.5.1.
	4 ≥75% decrease in pretreatment value OR any platelet count <20,000/mm^3; 20.0 x 10^9/L.	Consider transfusion for platelet count <10,000/mm3; <10.0 x 10^9/L. Consider further workup for immune thrombocytopenia and disease progression, including if needed bone marrow examination.	For ibrutinib, drug should be held until resolved to baseline or to grade 1. Follow the dose reductions described in Table 5. For zanubrutinib, hold study treatment if Grade 4 thrombocytopenia lasts

Toxicity	Grade (per CTCAE 4.03 or Hallek et al, 2008)	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		Consider holding any other anti-platelet therapy or anticoagulation as clinically indicated.	for more than 10 days and is assessed to be related to drug. Follow the dose reductions described in Section 6.5.1.
Bleeding	≥ Grade 3 bleeding not considered related to study drug	Intervention per institutional guidelines. Consider holding any other anti-platelet therapy or anticoagulation as clinically indicated. If bleeding is considered related to study drug and bleeding requires hospitalization, platelet transfusion may be of benefit if given at least 3-4 hr after last dose of drug, except for patients with CNS bleeding [Shatzel JJ et al, J Thomb Hemostat 2017].	Hold until recovery to ≤ Grade 1. Restart 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. If the underlying condition can be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of a re-bleed is deemed acceptable by the medical monitor, treatment may restart at dose level (-1). Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.
Other ≥ Grade 3 toxicity considered related to study drug, including inadequately controlled hypertension (HTN) and/or liver or renal laboratory value abnormalities	≥ 3		Follow dose reductions described in Section 6.5.1 for zanubrutinib and Section 6.5.2 for ibrutinib.

[redacted]

4. [redacted]

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Amendment 1 (04 August 2018)

No patients were enrolled before Amendment 1 of the protocol.

- Revised the inclusion criteria 9c: increased the upper limit of serum bilirubin to 3.0.
- Revised exclusion criteria 11a of HBV reactivation monitoring.
- Initial confirmation of progressive disease assessed by CT was sufficient for patients with SLL.

Amendment 2 (29 August 2019)

- Updated background information of zanubrutinib, including nonclinical data, clinical pharmacology, preliminary efficacy and safety data.
- Added "overall response rate determined by investigator assessment" as one of the secondary objectives and endpoints.
- [redacted]
- Updated study duration from [redacted] years to [redacted] months.
- Updated study drug access at study closure to clarify patients who benefit from zanubrutinib or ibrutinib may enroll in Zanubrutinib Long-Term Extension Study.
- Revision of inclusion criteria:
  - Removed inclusion criteria 3 e: Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.
  - Revised inclusion criteria 5: An extranodal lesion measure > 10 mm in longest perpendicular diameter would be defined as measurable disease.
  - Added note to inclusion criteria 8a: 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 and at least 7 days following the most recent administration of other myeloid growth factors (eg, G-CSF, GM-CSF).
  - Revised the inclusion criteria 8b: the lower limit of platelet count was changed to 30,000/mm^3 for patients with CLL.
  - Added the inclusion criteria 8c: hemoglobin ≥ 7.5 g/dL (may be post-transfusion).
- Revision of exclusion criteria:
  - Revised exclusion criteria 16: changed the criteria for ongoing corticosteroid use.

  - Added exclusion criteria 25: Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (eg, idiopathic thrombocytopenia purpura) requiring treatment.

- Added patients must sign an informed consent form before any screening procedures are conducted.
- Revision of Safety Follow-up Visit to End-of-Treatment Visit. Clarified the separation of Long-term Follow-up and Survival follow-up. Changes were made throughout the document.
- Revised efficacy assessments including primary endpoint.
- Revised CT assessment.
- Revised bone marrow examination.
- [redacted]
- Added laboratory assessments may be done with either central or local laboratory; same should be used throughout the study. The contents of applicable laboratory tests were revised accordingly.
- Added HIV testing
- Added assessment of del17p and cytogenetics, [redacted] *TP53* mutation and other molecular analysis.
- [redacted]
- Updated information of ibrutinib for administration, dose reduction/modification per local labeling.
- Revised guidelines to follow for dose interruption or modification of zanubrutinib.
- Added toxicity management recommendations.
- Updated information for serious adverse events for reporting and record.
- Deleted the appendix of medication known to prolong QT interval.

Amendment 3 (31 January 2020)

Key changes to the conduct of the study implemented with Amendment 3 were as follows:

- Increase the sample size from approximately 400 patients to approximately 600 patients.
- Updated study duration to approximately [redacted] months.
- Clarified that the CT or MRI will be performed as specified per the Schedule of Assessments (Appendix 10)**,** independent of possible study drug hold.
- [redacted]

- Added information on warnings and precautions for zanubrutinib.
- Revised zanubrutinib dose reduction for nonhematologic toxicity.
- Revised the summary of tumor lysis syndrome events in clinical studies for permitted medications.
- Revised the summary for the primary endpoint (overall response rate) analysis to state that overall response rate will be assessed by investigator, [redacted]
- Revised the summary for the key secondary endpoint (PFS) analyses to state that PFS was assessed by investigator, [redacted]
- Updated the noninferiority and superiority testing analysis summary for the primary endpoint (overall response rate)
- Updated analysis summary for key secondary endpoint (PFS) to remove the interim analysis and state that a single analysis will be performed.
- Deleted summary of planned sensitivity analyses for the primary efficacy endpoint (overall response rate) and the key secondary endpoint (PFS).
- Added to the note of Appendix 2 and Appendix 3 that patient may continue study treatment post first assessed PD due to drug hold if it is perceived that the patient will benefit from continued treatment.

BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	**BGB-3111-305**
Study Protocol Title:	**A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma**
Date:	March 12, 2021
Version:	Final 1.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADaM	Analysis data model
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration time curve
BID	Twice a day
BMI	Body mass index
BOR	Best overall response
BTK	Bruton's tyrosine kinase
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
CSR	Clinical study report

CT	Computed tomography
DBP	Diastolic blood pressure
DIPP	Data integrity protection plan
DOR	Duration of response
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EDC	Electronic data capture
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival

[redacted]	[redacted]
PR	Partial response
PR-L	Partial response with lymphocytosis
PT	Preferred term
Q1, Q3	First quartile, third quartile
QD	Once daily
QT	Electrocardiographic interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SE	Standard error
SLL	Small lymphocytic lymphoma
SOC	System organ class
SPD	Sum of products of the perpendicular diameters
SD	Stable disease
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum observed plasma concentration

TTR	Time to response
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the detailed plans for the analysis of safety and efficacy data for study BGB-3111-305: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. This SAP describes analyses for Europe and other regions outside of the United States and China; analyses for the United States and China will be covered in a separate SAP.

This document is based on the protocol version 3.0 dated 31JAN2020. [redacted]

2 STUDY OVERVIEW

This is a Phase 3, randomized open-label study of zanubrutinib versus ibrutinib in approximately 600 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The primary efficacy endpoint is overall response rate (ORR), defined as a best overall response of partial response (PR) or higher, per investigator assessment. Disease response will be assessed per the "modified" 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2008), with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL, and per Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) for patients with SLL. Rate of response for partial response with lymphocytosis (PR-L) or higher will be assessed as a secondary efficacy endpoint.

The study is broken into three periods for every patient:

- Screening Period
- Treatment Period
- Post-Treatment Period
    - End of Treatment Visit
    - Long-Term Follow-up
    - Survival Follow-up

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

Randomization will be stratified by age (<65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent).

Study treatment will be open-label and should continue until disease progression is confirmed by independent central review. The study duration is estimated to be approximately [redacted] months.

Assessments to be performed during the study include [redacted]; disease-related constitutional symptoms; physical examination of the liver, spleen and lymph nodes; computed tomography (CT) or protocol allowed alternative imaging modality scan of neck, chest, abdomen and pelvis with contrast; bone marrow examination at screening, for patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CRi [redacted]; patient-reported outcomes (PRO; European quality of life 5-dimensions 5-levels health questionnaire [EQ-5D-5L], European Organisation for Research and Treatment of Cancer quality of life cancer core questionnaire [EORTC QLQ-C30], [redacted]; laboratory studies; bone marrow examination; genetic alterations in the tumor cells (eg, del 17p, TP53, del 11q, del 13q, trisomy 12 and immunoglobulin variable region heavy chain [IGHV] mutation analysis).

Assessments of safety will include adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, electrocardiograms, ECOG performance status, and vital signs. Adverse events will be graded for severity per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and the Grading Scale for Hematologic Toxicities in CLL Studies according to Hallek 2008. An independent Data Monitoring Committee will periodically monitor safety data and perform the interim efficacy analysis.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by ORR determined by investigator

3.2 SECONDARY OBJECTIVES

- To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
  - Progression-free survival (PFS) determined by investigator assessment and independent central review
  - ORR determined by independent central review
  - Duration of response (DOR) determined by independent central review
  - DOR determined by investigator assessment
  - Time to treatment failure
  - Rate of PR-L or higher determined by independent central review
  - Overall survival
  - Health Related Quality of Life (HRQoL)
- To compare the safety of zanubrutinib versus ibrutinib

[redacted]

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINT

The primary endpoint is ORR (PR or higher, defined as CR/CRi + PR + nodular PR) per investigator assessment using the "modified" 2008 IWCLL guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL.

4.2 SECONDARY ENDPOINTS

Key Secondary Endpoints:

The key secondary endpoints are PFS per investigator assessment and atrial fibrillation/flutter incidence.

PFS is defined as the time from randomization to the date of first documentation of disease progression or death, whichever comes first.

For atrial fibrillation/flutter incidence, patients will be considered as having an atrial fibrillation/flutter event if they have a treatment-emergent AE of either "atrial fibrillation" or "atrial flutter".

Other Secondary Endpoints:

- ORR by independent central review
- PFS by independent central review
- DOR, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever comes first, determined by independent central review
- DOR by investigator assessment
- Time to treatment failure, defined as the time from randomization to discontinuation of study drug due to any reason
- Rate of PR-L or higher, defined as the proportion of patients who achieve a CR/CRi + PR + nodular PR + PR-L determined by independent central review

- Rate of PR-L or higher determined by investigator assessment
- Overall survival, defined as the time from randomization to the date of death due to any cause
- HRQoL measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs

[redacted]

5 SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on the primary efficacy analyses for the primary endpoint of ORR per investigator assessment. Assuming a response ratio (zanubrutinib arm / ibrutinib arm) of 1.03 (72% / 70%), 600 patients will provide more than 90% power to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 0.8558 (response ratio) and a 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction. The response rate for ibrutinib is approximated from published clinical data (Byrd et al 2019).

Assuming a hazard ratio (HR) of 0.9 (zanubrutinib arm / ibrutinib arm), 205 PFS events are required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 1.3319 (HR) for the key secondary endpoint of PFS per investigator assessment. [redacted] A median PFS of [redacted] months for ibrutinib and an exponential distribution for PFS are also assumed.

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

The Intent to Treat (ITT) Analysis Set includes all randomized patients.

The Safety Analysis Set includes all patients who received any dose of study drug. The Safety Analysis Set will be used for all safety analyses.

The Per-protocol Analysis Set includes patients who received any dose of study drug and had no critical protocol deviation. Categories of critical protocol deviations are defined in Section 6.3.2.

Criteria for exclusion from the Per-protocol Analysis Set will be determined and documented before the database lock for the interim analysis of the primary endpoint.

[redacted]

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

Descriptive statistics include n, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables and n (%) for categorical variables.

If an event date (eg, AE onset date) is partial or missing, the date will appear partial or missing in the listings.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2.1 Definitions and Computations

Study treatment (study drug): Study drug for this study is zanubrutinib or ibrutinib.

Study day: Study day will be calculated relative to the date of the first dose of study drug (study day 1). For patients not dosed, the randomization date will be used instead of the first dose date. For assessments conducted on or after the date of first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

Treatment duration: The treatment duration will be calculated as (date of last dose of study drug – date of first dose of study drug + 1).

Baseline: the baseline value or assessment is defined as the last non-missing value or assessment before the first dose of study drug or before randomization for patients not dosed.

Postbaseline: a postbaseline value or assessment is defined as a value or assessment after the first dose of study drug or after randomization for patients not dosed.

6.2.2 Handling of Missing Data

Missing data will not be imputed unless otherwise specified. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures as provided in Appendix A: Imputation of Missing or Partially Missing Dates. Missing data for the health-related quality-of-life (HRQoL) data will be handled according to each PRO instrument manual (Fayers & Machin, 2000 in The EORTC QLQ-C30 (Third Edition), 2001; https://euroqol.org/publications/user-guides/).

Missing longitudinal data analyses may employ the missing-at-random (MAR) assumption such as described for QLQ-C30 scores over time in Section 6.4.2.3.9.

Time-to-event data analyses will have associated censoring rules as described for PFS in Section 6.4.2.1.

When summarizing categorical variables, patients with missing data are generally included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented.

When summarizing continuous variables, patients with missing data are not included in calculations unless otherwise specified.

6.2.3 Adjustment for Covariates

Stratified analysis will be performed to adjust for important baseline covariates for the primary and some secondary endpoints. Details of the stratified analyses are provided in Section 6.4.

6.2.4 Multiplicity Adjustment

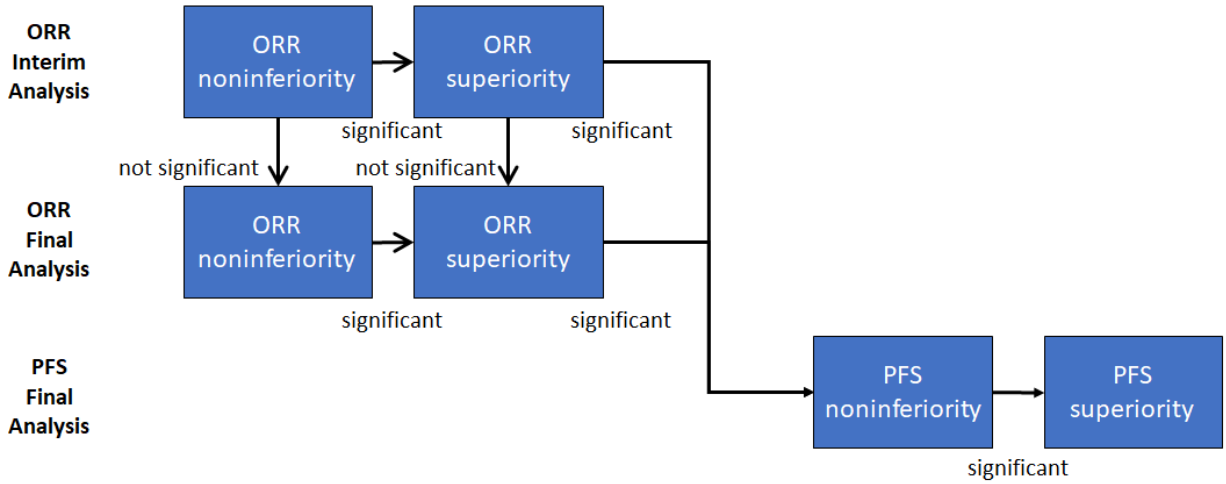
To control the study-wide type I error, individual significance levels will be adjusted for the tests of the primary endpoint of ORR per investigator assessment (noninferiority and superiority), and

the key secondary endpoint of PFS per investigator assessment (noninferiority and superiority). Multiplicity due to multiple endpoints and multiple tests will be handled per the graphical approach by Maurer and Bretz (2013) utilizing fixed sequence hierarchical testing. Under this procedure, secondary endpoints will be tested only if the primary endpoint is significant.

If the noninferiority of ORR per investigator assessment is statistically significant, the key secondary endpoint of atrial fibrillation/flutter incidence will be tested at the interim and final analyses of ORR with the same 1-sided significance levels as ORR but will be tested separately from the fixed sequence hierarchical testing.

Hypothesis testing will be performed according to the multiplicity adjustment flowchart shown in Figure 1.

Figure 1. Flowchart for the Multiplicity Adjustment



Per the testing sequence in Figure 1, the study-wide 1-sided significance level of 0.025 will be passed to subsequent hypothesis tests in the sequence and will be distributed for each of the following potential analysis timepoints based on the known correlation of the interim and final test statistics and corresponding alpha spending function:

- interim analysis of ORR
    - noninferiority of ORR per investigator assessment is tested at a 1-sided significance level of 0.005 based on the O'Brien-Fleming alpha spending function

with an information fraction of 64% (415 divided by 652, total number of randomized patients); if this is not statistically significant, do not conduct any of the remaining hypothesis tests at this analysis timepoint and continue to the final analysis of ORR

- if the noninferiority of ORR per investigator assessment is statistically significant, the superiority of ORR per investigator assessment will be tested at a 1-sided significance level of 0.005 based on the O'Brien-Fleming alpha spending function with an information fraction of 64%; if this is not statistically significant, continue to the final analysis of ORR for additional hypothesis testing starting with the superiority of ORR per investigator assessment
- if the superiority of ORR per investigator assessment is statistically significant at the interim analysis, PFS per investigator assessment will be compared between the two treatment arms for descriptive purposes only, but not for statistical inference (for either non-inferiority or superiority) at this interim analysis. A 1-sided 0.00001 significance level will be spent to account for the increased false positive rate due to this descriptive analysis.

- final analysis of ORR
  - if the noninferiority of ORR per investigator assessment was not statistically significant at the interim analysis of ORR,
    1. noninferiority of ORR per investigator assessment will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, the study does not meet the primary objective and no additional hypothesis testing will be performed in this study
    2. if the noninferiority of ORR per investigator assessment is statistically significant, the superiority of ORR per investigator assessment will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, no additional hypothesis testing will be performed in this study
    3. if the superiority of ORR per investigator assessment is statistically significant, PFS per investigator assessment will be compared between the two treatment arms for descriptive purposes only, but not for statistical

inference (for either non-inferiority or superiority). A 1-sided 0.00001 significance level will be spent to account for the increased false positive rate due to this descriptive analysis.

- if the noninferiority of ORR per investigator assessment was statistically significant but the superiority of ORR per investigator assessment was not significant at the interim analysis of ORR
  1. the superiority of ORR per investigator assessment will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, no additional hypothesis testing will be performed in this study
  2. if the superiority of ORR per investigator assessment is statistically significant, PFS per investigator assessment will be compared between the two treatment arms for descriptive purposes only, but not for statistical inference (for either non-inferiority or superiority). A 1-sided 0.00001 significance level will be spent to account for the increased false positive rate due to this descriptive analysis.

- final analysis of PFS
  - if the superiority of ORR per investigator assessment is statistically significant at either the interim or final analysis of ORR, PFS per investigator assessment will be followed further until 205 PFS events per investigator assessment have occurred for the final PFS analysis; noninferiority of PFS per investigator assessment will be first tested at a 1-sided significance level of 0.02498
  - if the noninferiority of PFS per investigator assessment is statistically significant, the superiority of PFS per investigator assessment will be tested at a 1-sided significance level of 0.02498.

6.2.5 Data Integrity

Before pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All essential data

should be complete and reviewed up to a pre-specified cutoff date. Critical consistency checks and appropriate source data verification should be completed according to the final data extraction plan.

Though the study is open-label, access to study data is controlled for specific sponsor study team members overseeing the conduct of the study or analyzing study data. The sponsor will not have access to aggregated efficacy or safety data summaries by treatment arm according to the study's Data Integrity Protection Plan (DIPP).

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The following patient disposition information will be summarized by treatment arm:

- Number of randomized patients
- Number (%) of treated patients
- Number (%) of treated patients still receiving treatment as of the data cutoff
- Number (%) of treated patients who discontinued treatment and reasons for treatment discontinuation
- Number (%) of randomized patients still on study as of the data cutoff
- Number (%) of randomized patients who discontinued study and reasons for study discontinuation

Study follow-up time is defined as the time from the randomization to the death date or the end of study date for the patients who discontinued from study (whichever occurs first), or the data cutoff date for patients still on study. Study follow-up time will be summarized descriptively.

6.3.2 Protocol Deviations

Important protocol deviations are protocol deviations designated as "Major" or "Significant" per the China and the Rest of the World protocol deviation data, respectively.

Critical protocol deviations will also be identified and used to define the Per-protocol Analysis Set. Critical protocol deviations will be identified before the database lock. The critical protocol

deviations will include but are not limited to selected protocol deviations from the following categories:

- Patient randomized even though he/she did not satisfy study eligibility criteria
- Patient developed study drug withdrawal criteria but was not withdrawn
- Patient received wrong study treatment or incorrect dose
- Patient received prohibited concomitant treatment

Important protocol deviations and critical protocol deviations will be summarized by deviation category and by treatment arm. COVID-19-related protocol deviations will be summarized. A listing will also be provided.

6.3.3 Randomization Stratification Factors

The number of patients with each of the IRT randomization stratification factors will be summarized by treatment arm. The randomization stratification factors include age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent). In addition, stratification errors (defined as IRT-based strata vs clinical data-based strata inconsistencies) will be summarized.

6.3.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics including the following will be summarized by treatment arm using descriptive statistics:

- Age (years);
- Age group (< 65 vs ≥ 65 years);
- Sex;
- Race and ethnicity;
- Geographic region (Asia vs Australia/New Zealand vs Europe vs North America);
- Height (cm), weight (kg), and body mass index (BMI, kg/m^2);
- Eastern Cooperative Oncology Group (ECOG) performance status.

6.3.5 Disease History and Baseline Disease Characteristics

Baseline disease characteristics including the following will be summarized by treatment arm using descriptive statistics:

- Time since initial CLL/SLL diagnosis;
- Disease type (CLL vs SLL);
- Disease stage (Binet stage for CLL; Ann Arbor stage for SLL) at study entry;
- Bulky disease (any target lesion longest diameter ≥ 5 cm; ≥ 10 cm);
- Serum immunoglobulin (IgM, IgA and IgG);
- β2 microglobulin (quantitative and categorical: ≤ 3 mg/L vs > 3 mg/L);
- Hepatitis B core antibody and hepatitis C virus antibody statuses (positive vs negative);
- Coagulation parameters of prothrombin time, international normalized ratio, and aPTT (< LLN vs normal vs > ULN);
- Mutation statuses: del 17p, TP53, trisomy 12, del 11q, del 13q, IGHV;
- Splenomegaly (yes vs no);
- Hepatomegaly (yes vs no);
- Bone marrow involvement (< 30% vs ≥ 30%);
- ALC;
- Hemoglobin (quantitative and categorical: ≤ 110 g/L vs. > 110 g/L);
- Platelet (quantitative and categorical: ≤ 100 x 10^9/L vs. > 100 x 10^9/L);
- ANC (quantitative and categorical: ≤ 1.5 x 10^9/L vs. > 1.5 x 10^9/L);
- Any cytopenia (yes: hemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L or ANC ≤ 1.5 x 10^9/L vs no);
- LDH;
- Prior radiotherapy and prior transplants (yes vs no);
- Disease-related constitutional symptoms.

Categories of baseline characteristics can be modified depending on the availability of data and/or percentage of categories.

6.3.6 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0 or higher). The number and percentage of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class (SOC) preferred term (PT), and treatment arm. A listing of medical history will be provided.

6.3.7 Prior Systemic Anti-Cancer Therapies

Number of prior lines of systemic anti-cancer therapies, duration of last therapy, best response of last therapy, and time since the end of last therapy will be summarized for prior anti-cancer therapy by treatment arm using descriptive statistics. The therapies with the same sequence/line number are counted as one prior line of therapy. A listing of these therapies will be provided.

6.3.8 Prior and Concomitant Medications, Procedures and Surgeries

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes version March 2017 or later and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

Prior medications are defined as medications that started before the first dose date. Concomitant medications are defined as medications that (1) started before the first dose of the study drug and were continuing at the time of the first dose of the study drug, or (2) started on or after the first dose date of the study drug up to 30 days after the last dose date or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first.

The number and percentage of patients reporting prior medications and concomitant medications will be summarized by ATC medication class Level 2, WHO DD preferred name, and treatment arm. A listing of the prior and concomitant medications will be provided.

In addition, the number and percentage of patients reporting postbaseline anti-cancer therapies will be summarized by WHO DD preferred name, and treatment arm. The number and percentage of patients reporting postbaseline cancer-related surgery or procedures will be summarized by treatment arm. A listing of procedures and surgeries will be provided.

6.4 EFFICACY ANALYSES

Statistical testing will be performed to compare the efficacy of zanubrutinib (Arm A) and ibrutinib (Arm B). For all efficacy analyses, patients will be analyzed according to the treatment

arm to which they were randomized, and unless otherwise specified, efficacy analyses will be performed on the ITT Analysis Set. At the interim analysis of ORR, ORR, DOR and associated descriptive analyses will be performed on the first 415 randomized patients in the ITT Analysis Set.

Dates for investigator disease assessments are derived according to Appendix B, and best overall response derivation rules for CLL are derived according to Appendix C.

ORR, rate of PR-L or higher and rate of CR/CRi will be based on the best overall response (BOR), and BOR per investigator assessment and per independent central review will be subject to confirmation for CLL patients as detailed in Appendix C and in the separate independent review charter. BOR is defined as the best response from the randomization date to the data cutoff date, disease progression or the start of new CLL/SLL therapy, whichever comes first. Patients without any postbaseline disease assessment (regardless of the reason) will be considered as non-responders.

Stratified analyses will be based on the randomization stratification factors per IRT unless otherwise specified.

6.4.1 Primary Efficacy Analyses

The primary hypothesis testing for the primary endpoint of ORR per investigator assessment will be to demonstrate the noninferiority of zanubrutinib to ibrutinib.

Noninferiority testing for ORR

The null and alternative hypotheses for the noninferiority test are as follows:

- H_{0NI}: Response ratio (zanubrutinib/ibrutinib) ≤ 0.8558
- H_{aNI}: Response ratio (zanubrutinib/ibrutinib) > 0.8558

One interim analysis of ORR will occur approximately 12 months after 415 patients have been randomized, and the final analysis of ORR will occur approximately 12 months after 600 patients have been randomized.

The monitoring boundaries for the noninferiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025. Hypothesis testing for the noninferiority of ORR at the interim analysis will be based on

the first 415 randomized patients only and will have a 1-sided significance level of 0.005. Hypothesis testing for the noninferiority of ORR at the final analysis will be based on the entire ITT Analysis Set and will have a 1-sided significance level based on the actual information fraction (or covariance) of the interim and final test statistics. With 652 patients in the ITT Analysis Set at the final analysis, the actual information fraction is 64% (415/652), and the 1-sided significance level for the final analysis will be 0.0235.

The noninferiority hypothesis of ORR will be tested at each analysis using a stratified Wald test against a null response ratio of 0.8558, and the noninferiority of zanubrutinib to ibrutinib in ORR will be considered statistically significant if the 1-sided p-value is less than the 1-sided significance level at either the interim or the final analysis of ORR. The form of the Wald statistic (Z) will be as follows:

$$Z = \frac{\log(\rho) - \log(0.8558)}{\mathrm{SE}(\log(\rho))}$$

where log(ρ) is the log of the stratified Mantel-Haenszel response ratio estimate and SE(log(ρ)) is its corresponding standard error estimate (Greenland and Robins 1985)

Table 1 summarizes the interim and final analysis monitoring boundaries for ORR noninferiority and superiority testing with 64% information fraction.

Table 1. ORR Monitoring Boundaries

Analysis Timepoint	ORR Noninferiority		ORR Superiority	
	1-sided p-value boundary	Approximate response ratio boundary [1]	1-sided p-value boundary	Approximate response ratio boundary [1]
Interim Analysis of ORR	0.005	1.01	0.005	1.176
Final Analysis of ORR	0.0235	0.952	0.0235	1.105

[1] Approximate boundary based on assumed ibrutinib ORR of 70%.

Justification of the noninferiority margin for ORR

A non-inferiority margin of 0.8558 in response ratio was derived using the 95% to 95% fixed margin approach (FDA Guidance for Industry Non-Inferiority 2016). In the RESONATE trial (Byrd et al 2014), the ibrutinib effect over ofatumumab represented by the ratio of response rate (PR or higher) was 10.43 with a 95% CI of (5.2, 21.0) based on the independent review committee assessment. Thus, M1 is 5.2, the lower bound of the 95% CI. Since the effect size of ibrutinib is versus an active control (ofatumumab), rather than placebo, the choice of M1 is conservative, and a non-inferiority margin of 0.8558 (for the response ratio) retains over 90% of M1 (on the log scale).

Superiority testing for ORR

As described in Section 6.2.4, if the noninferiority in ORR per investigator assessment is statistically significant, then the superiority of zanubrutinib to ibrutinib in ORR will be tested. The null and alternative hypotheses for the superiority test are as follows:

- H_{0SUP}: Response ratio (zanubrutinib/ibrutinib) ≤ 1
- H_{aSUP}: Response ratio (zanubrutinib/ibrutinib) > 1

The monitoring boundaries for the superiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025. If hypothesis testing for the superiority of ORR is performed at the interim analysis, it will be based on the first 415 randomized patients only and will have a 1-sided significance level of 0.005. If hypothesis testing for the superiority of ORR is performed at the final analysis, it will be based on the entire ITT Analysis Set and will have a 1-sided significance level that depends on the actual information fraction (or covariance) of the interim and final test statistics and will be the same 1-sided significance level used for the noninferiority ORR testing (0.0235, equivalent to a chi-squared p-value cutoff of 0.0469).

The superiority hypothesis of ORR will be tested using a stratified Cochran-Mantel-Haenszel test, and the superiority of zanubrutinib to ibrutinib in ORR will be considered statistically significant if the 1-sided p-value is less than the 1-sided significance level at either the interim or the final analysis of ORR.

Additional descriptive analyses

The 95% confidence interval (CI) for the response ratio will be constructed using a normal approximation. ORR will be summarized for each treatment arm along with its corresponding 95% CI.

Time to response, defined as the time from randomization to the earliest qualifying response, will be summarized descriptively for responders only.

Best overall response (BOR) will be summarized as well. In addition, the concordance between independent central review and investigator assessment of BOR will be summarized.

The rate of CR/CRi will be summarized for each treatment arm along with its corresponding 95% CI.

At the interim analysis of ORR only, the above descriptive analyses will be performed on the first 415 randomized patients in the ITT Analysis Set and BOR will also be summarized for the entire ITT Analysis Set.

6.4.2 Secondary Efficacy Analyses

The key secondary endpoints are PFS per investigator assessment and atrial fibrillation/flutter incidence. For the other secondary endpoints, the tests will be descriptive without multiplicity adjustment.

6.4.2.1 Key secondary endpoint: Progression-free Survival per investigator assessment

Hypothesis testing for the key secondary endpoint of PFS will first be to demonstrate the noninferiority of zanubrutinib to ibrutinib.

There will be a single analysis of PFS for the purpose of inference when approximately 205 PFS events have occurred; however, a 1-sided significance level of 0.00001 will be applied to each of the two descriptive analyses of PFS for the interim and final analyses of ORR to compensate for the potential type I error increase from the descriptive analysis. From the time of the ORR analyses to the analysis of PFS after 205 events have occurred, the sponsor will continue to maintain trial integrity according to the DIPP.

PFS will be right-censored for patients who meet one of the following conditions: 1) no baseline disease assessments; 2) PD or death more than 6 months from the last disease assessment (more than 12 months if a patient is on the disease assessment schedule of every 24 weeks); and 3) alive without documentation of PD. The censoring convention generally follows the FDA

Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018) and references within the guidance document. The censoring rules are summarized in Table 2.

Table 2. Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression or Censoring	Outcome
Death or PD between the planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Event
Death before the first disease assessment	Date of death	Event
No baseline/postbaseline disease assessments (and no death)	Date of randomization	Censored
Death or PD more than 6 months [1] from the last disease assessment	Date of the last disease assessment before death or PD	Censored
Alive without documentation of PD	Date of last disease assessment	Censored

[1] 12 months if a patient is on the assessment schedule of every 24 weeks.

Noninferiority testing for PFS per Investigator Assessment

The null and alternative hypotheses for the noninferiority test are as follows:

- H_{0NI}: HR (zanubrutinib/ibrutinib) $\geq$ 1.3319
- H_{aNI}: HR (zanubrutinib/ibrutinib) $<$ 1.3319

At the final analysis of PFS, hypothesis testing for the noninferiority of PFS per investigator assessment will be based on the entire ITT Analysis Set using a stratified Wald test and will have a 1-sided significance level of 0.02498. The form of the Wald statistic (Z) will be as follows:

$$Z = \frac{\beta - \log(1.3319)}{\mathrm{SE}(\beta)}$$

where β is the log of the hazard ratio estimate from the stratified Cox proportional hazards model and SE(β) is its corresponding standard error estimate

Justification of the noninferiority margin for PFS

A non-inferiority margin of 1.3319 was derived using the 95% to 95% fixed margin approach based on the RESONATE study. In the updated RESONATE results (Brown et al 2014), the estimated PFS HR for ibrutinib versus ofatumumab was 0.106 with a 95% CI of (0.073, 0.153). Therefore, the control arm effect (M1) is 0.153 in HR and -1.877 in log HR. A noninferiority margin of 1.3319 for the HR (zanubrutinib/ibrutinib) retains approximately 85% of M1 (on the log scale).

Superiority testing for PFS per Investigator Assessment

If the noninferiority of zanubrutinib to ibrutinib in PFS per investigator assessment is statistically significant, then the superiority in PFS per investigator assessment will be tested. The null and alternative hypotheses for the superiority test are as follows:

- H_{0SUP}: HR (zanubrutinib/ibrutinib) ≥ 1
- H_{aSUP}: HR (zanubrutinib/ibrutinib) < 1

Hypothesis testing for the superiority of PFS per investigator assessment will be based on the entire ITT Analysis Set using a stratified log-rank test and will have the same 1-sided significance level of 0.02498 (equivalent to a chi-squared p-value cutoff of 0.04996) used for the noninferiority PFS testing.

Additional descriptive analyses

The HR for PFS and its 95% CI will be estimated from a stratified Cox regression model.

The distribution of PFS, including the median and other quartiles, and the PFS rate at selected timepoints such as 12, 18 and 24 months, will be estimated using the Kaplan-Meier method for each treatment arm. The 95% CI for the median and the other quartiles of PFS will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley 1982). The 95% CI for the

PFS rate at the selected timepoints will be estimated using the Greenwood formula (Greenwood 1926). The duration of follow-up for PFS will be estimated using the reverse Kaplan-Meier method (Schemper and Smith 1996).

Kaplan-Meier curves for PFS will be presented for each treatment arm. A listing of PFS-related information, eg, the date of the progression or censoring and the corresponding reasons, will also be provided.

6.4.2.2 Key secondary endpoint: Atrial fibrillation/flutter incidence

As described in Section 6.2.4, if the noninferiority of zanubrutinib to ibrutinib in ORR is statistically significant, then the superiority of zanubrutinib to ibrutinib in the key secondary endpoint of atrial fibrillation/flutter will be tested but separately from the fixed sequence hierarchical testing that includes ORR and PFS. The interim analysis will be performed on the Safety Analysis Set restricted to the first 415 randomized patients and according to the actual treatment received. The final analysis will be performed on the Safety Analysis Set according to the actual treatment received.

The monitoring boundaries for the superiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025. If hypothesis testing for the superiority of the rate of atrial fibrillation/flutter is performed at the interim analysis, it will have a 1-sided significance level of 0.005 (equivalent to a chi-squared p-value cutoff of 0.0099). If hypothesis testing for the superiority of the rate of atrial fibrillation/flutter is performed at the final analysis, it will have a 1-sided significance level of 0.0235 (equivalent to a chi-squared p-value cutoff of 0.0469).

Hypothesis testing on the rate of atrial fibrillation/flutter will be performed using an unstratified chi-squared test if the expected counts in the 2 x 2 contingency table (treatment arm by atrial fibrillation/flutter status) are at least 5 patients. If any expected count in the 2 x 2 contingency table is less than 5 patients, then hypothesis testing will be performed using Fisher's exact test.

6.4.2.3 Other secondary endpoints

6.4.2.3.1 ORR per Independent Central Review

ORR per independent central review will be summarized and analyzed using the same methods used for ORR per investigator assessment.

6.4.2.3.2 PFS per Independent Central Review

PFS per independent central review will be summarized and analyzed using the same methods used for PFS per investigator assessment.

6.4.2.3.3 Duration of Response (DOR) by Independent Central Review

DOR by independent central review will be analyzed only for patients in the ITT Analysis Set who achieved a response (PR or higher) per independent central review. At the interim analysis of ORR only, DOR by independent central review will be analyzed only for the first 415 randomized patients in the ITT Analysis Set who achieved a response (PR or higher) per independent central review.

The censoring conventions and the analyses of DOR by independent central review will be the same as those of PFS with the exception that treatment arm comparisons will not be performed, ie, no HR or corresponding CI or testing will be calculated or performed.

6.4.2.3.4 DOR by Investigator Assessment

DOR by investigator assessment will be analyzed only for patients in the ITT Analysis Set who achieved a response (PR or higher) per investigator assessment. At the interim analysis of ORR only, DOR by investigator assessment will be analyzed only for the first 415 randomized patients in the ITT Analysis Set who achieved a response (PR or higher) per investigator assessment.

Analyses of DOR will be repeated based on the investigator assessment with the same methods as those for DOR by independent central review.

6.4.2.3.5 Time to Treatment Failure

The HR for time to treatment failure and its 95% CI will be estimated from a stratified Cox regression model.

The distribution of time to treatment failure, including the median and other quartiles, and the on-treatment rate (ie, no treatment failure) at selected timepoints such as 12, 18 and 24 months, will be estimated using the Kaplan-Meier method for each treatment arm. The 95% CI for the median and the other quartiles of time to treatment failure as well as the on-treatment rate at the selected timepoints will be estimated as for PFS. Time to treatment failure will be censored at the data cutoff for patients who did not discontinue.

6.4.2.3.6 Rate of PR-L or Higher by Independent Central Review

The rate of PR-L or higher by independent central review will be summarized for each treatment arm along with its corresponding 95% CI. At the interim analysis of ORR only, the rate of PR-L or higher by independent central review will be analyzed only for the first 415 randomized patients in the ITT Analysis Set.

6.4.2.3.7 Rate of PR-L or Higher per Investigator Assessment

The rate of PR-L or higher per investigator assessment will be summarized for each treatment arm along with its corresponding 95% CI. At the interim analysis of ORR only, the rate of PR-L or higher per investigator assessment will be analyzed only for the first 415 randomized patients in the ITT Analysis Set.

6.4.2.3.8 Overall Survival

Patients who remained alive as of the data cutoff or discontinued study due to reasons other than death will be right censored at the date on which the patient was last known to be alive. The methods and analyses for overall survival will be the same as those described for PFS.

6.4.2.3.9 Health Related Quality of Life

The scoring of the EORTC QLQ-C30 and EQ-5D-5L will follow their corresponding manuals (Fayers et al. 2001; EuroQol Group 1990; Herdman et al 2011).

EORTC QLQ-C30

The scores of the EORTC QLQ-C30 questionnaire will be summarized at each assessment timepoint for each treatment arm. Summaries will include: scores and changes from baseline in the QLQ-C30 global health status/QoL (GHS/QoL) scale and the five functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), three Symptom scales (fatigue, pain, and nausea and vomiting), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

Higher QLQ-C30 symptom scales and single item scores indicate worse HRQoL. Higher scores in the functional scales and GHS/QoL scale indicate better HRQoL.

In addition, the change from baseline in QLQ-C30 GHS/QoL scale scores will be compared between treatment arms using a linear mixed model for repeated measures (MMRM) at the predefined timepoints of Cycle 7 (24 weeks) and Cycle 13 (48 weeks). The model will include the repeated measurement (for Cycles 4, 7, 10 and 13) of the change from baseline in QLQ-C30

GHS/QoL score as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with either an unstructured covariance matrix (Mallinckrodt 2018) or a simpler covariance structure, eg, heterogeneous Toeplitz. The difference between treatment arms in change from baseline score at Cycles 7 and 13 as well as their 95% CIs will be estimated, and the corresponding p-values will be presented.

EQ-5D-5L

The EQ-5D-5L comprises a descriptive system and an EQ Visual Analogue Scale (EQ VAS) with the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 0 to 100 scale, with 100 labelled 'the best health you can imagine' and 0 'the worst health you can imagine'.

EQ VAS will be summarized descriptively by treatment arm at each assessment timepoint. Descriptive statistics will also be provided by treatment arm at each assessment timepoint including the number and percentage of patients reporting each level of problem on each dimension of the EQ-5D-5L.

6.4.3 Sensitivity Analyses

Primary endpoint of ORR

The noninferiority of the primary endpoint of ORR will also be analyzed in the Per-protocol Analysis Set.

A sensitivity analysis of ORR using an alternative set of response confirmation rules (see Appendix C) will be performed that allows PR-L to be subsequently confirmed as a best overall response of PR.

To account for disease progression due to study drug interruption, ORR and BOR will be summarized based on all disease assessments through the data cutoff date, disease progression or the start of new CLL/SLL therapy, whichever comes first; however, disease progression that occurs within 6 weeks of a study drug interruption of at least 7 days will not be counted as disease progression for the purpose of this sensitivity analysis.

To account for the impact of COVID-19, ORR will be summarized for each treatment arm excluding patients who have died due to COVID-19.

Key secondary endpoint of PFS

The non-inferiority of the key secondary endpoint of PFS will also be analyzed in the Per-protocol Analysis Set.

Alternative censoring rules such as censoring for new CLL/SLL therapies will be applied as another sensitivity analysis of PFS.

To account for disease progression due to study drug interruption, PFS will also be summarized where disease progression that occurs within 6 weeks of a study drug interruption of at least 7 days will not be counted as disease progression for the purpose of this sensitivity analysis.

To account for the impact of COVID-19, PFS will be summarized for each treatment arm while additionally censoring deaths due to COVID-19.

6.4.4 Subgroup Analyses

The primary and selected secondary endpoints will be summarized, as appropriate, in the following subgroups (if collected in both IRT and in the clinical data, clinical data including EDC will be used to define subgroups):

- Age group (< 65 vs ≥ 65 years);
- Sex;
- Geographic region (Asia vs Australia/New Zealand vs Europe vs North America);
- Prior lines of therapy (1-3 vs > 3);
- Baseline ECOG performance status (0 vs ≥ 1);
- Baseline del17p/TP53 mutation status (present or absent);
- Bulky disease (yes: any target lesion longest diameter ≥ 5 cm vs no);
- Baseline β2 microglobulin (≤ 3 mg/L vs > 3 mg/L);
- Baseline IGHV mutation status (unmutated vs mutated);
- Disease stage (Binet stage of A/B and Ann Arbor stage I-II bulky vs Binet stage C and Ann Arbor stage III/IV) at study entry

When the sample size of a subgroup is too small, the subgroup may be omitted from the analyses or be combined with other subgroups if appropriate. Forest plots for the subgroup analyses will be provided with 95% CIs based on unstratified methods.

[redacted]

6.5 SAFETY ANALYSES

All safety analyses will be performed in the Safety Analysis Set.

Safety will be assessed by the monitoring and recording of all adverse events (AEs) graded by NCI-CTCAE v4.03. Laboratory values (complete blood count [CBC], serum chemistry, and coagulation), vital signs, physical exams, ECOG performance status and ECGs findings will also be used to assess safety. Descriptive statistics will be used to summarize the safety data by treatment arm.

For all safety analyses by treatment arm, patients will be analyzed according to the actual treatment received.

6.5.1 Extent of Exposure

The extent of exposure to study drug will be summarized descriptively by treatment arm as the number of cycles received (number and percentage of patients), treatment duration (months),

cumulative total dose received per patient (g), actual dose intensity (mg/day) and relative dose intensity (%).

The number and percentage of patients with dose reductions, dose interruption, and drug discontinuation will be summarized with the respective reasons.

The actual dose intensity is defined as the actual cumulative dose (mg) taken based on the total dose per day divided by the treatment duration (days). The relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity as a percentage where the planned dose intensity is 320 mg/day for zanubrutinib and 420 mg/day for ibrutinib.

Patient data listings will be provided for all dosing records.

6.5.2 Adverse Events

The AE verbatim descriptions (terms 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 the MedDRA (Version 20.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent. Only TEAEs will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

TEAEs will be summarized by treatment arm as the number and percentage of patients reporting TEAEs by SOC and PT. A patient will be counted only once within a system organ class and preferred term. TEAEs will also be summarized by grade and by the relationship to study drug assessed by the investigator, ie, treatment-related or not. A treatment-related AE is an AE that is assessed by the investigator as related to the study drug or is missing an assessment of the causal relationship. TEAEs summarized by grade or by relationship to study drug will be summarized at the maximum severity grade or strongest causal relationship to study drug, respectively.

No imputation of AE grades will be performed. Treatment-emergent adverse events (TEAEs) with missing CTCAE grade will only be summarized in the total column.

An overall summary of TEAEs will include the number and percentage of patients with at least one:

- TEAE;
- treatment-related TEAE;
- grade 3 or higher TEAE;
- treatment-related grade 3 or higher TEAE;
- TEAE leading to death;
- treatment-related TEAE leading to death;
- serious TEAE;
- treatment-related serious TEAE;
- TEAE leading to treatment discontinuation;
- treatment-related TEAE leading to treatment discontinuation;
- TEAE leading to dose modification;
- treatment-related TEAE leading to dose modification;
- TEAE leading to dose reduction;
- treatment-related TEAE leading to dose reduction;
- TEAE leading to dose interruption;
- treatment-related TEAE leading to dose interruption.

The summaries of the TEAEs will be provided by PT only, by SOC and PT, and by SOC, PT and maximum severity grade.

The adverse events of special interest (AESIs) will be defined and summarized by AESI category and PT for the following:

- treatment-emergent AESIs;
- grade 3 or higher treatment-emergent AESIs;
- serious treatment-emergent AESIs;
- treatment-emergent AESIs leading to treatment discontinuation;
- treatment-emergent AESIs leading to dose modification;

- treatment-emergent AESIs leading to dose reduction;
- treatment-emergent AESIs leading to dose interruption;
- treatment-emergent AESIs by maximum severity.

Time to first AESI along with cumulative event rates at milestone timepoints as well as patient incidence in 3-month intervals over time may be presented for selected AESIs.

TEAEs related to liver, arrythmia and diarrhea will be defined and summarized by category and PT for all such events, grade 3 or higher, serious and by maximum severity.

Incidence and time to diarrhea (grade 3 or higher), severe bleeding (defined as grade 3 or higher 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.

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be provided.

Listings of deaths, AEs, serious AEs, AEs leading to death, and AEs leading to dose modification or discontinuation of the study drug will be provided. In addition, a listing of serious AEs for patients with COVID-19 infection will be provided. No imputation will be done in the AE listings.

6.5.3 Laboratory Values

The values and changes from baseline for selected CBC components, serum chemistry and serum immunoglobulin parameters will be summarized by treatment arm at each assessment timepoint and for the worst postbaseline assessment.

Certain laboratory parameters can come from central or local laboratories (eg, hematology, chemistry). Summaries of laboratory parameters will be based on the preferred laboratory (central or local, not both) for each patient, and the preferred laboratory will be the central laboratory if central laboratory data are available and the local laboratory if central laboratory data are not available.

Laboratory parameters that are graded in NCI-CTCAE v4.03 will be summarized by the CTCAE grade and laboratory parameters that are graded per Hallek (2008) including platelets, hemoglobin and absolute neutrophil count will be summarized by the Hallek toxicity grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in

both high and low directions (eg, calcium, glucose, magnesium, phosphorus, potassium, sodium) will be summarized separately.

A summary of the number and percentage of patients with grade 3 or higher toxicity will be provided for selected laboratory parameters of interest. Shift tables assessing the toxicity grade at baseline versus the worst postbaseline toxicity grade recorded will be presented.

Hematology, serum chemistry, serum immunoglobulin and coagulation results for each patient will be presented in data listings. A listing of all grade 3 or higher laboratory values will also be provided.

Incidence of patients who met one or more of the Hy's law criteria will be summarized. A listing of patients that met one or more of the Hy's law criteria will be generated.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, weight) and changes from baseline will be presented by assessment timepoint. A listing by patient and assessment timepoint will be generated.

6.5.5 Electrocardiograms (ECG)

The QTc-Fridericia (QTcF) interval values and changes from baseline will be summarized by treatment arm for each assessment timepoint. If triplicate readings (eg, screening) are recorded, the average of the readings for the assessment timepoint will be used for the summary.

The number and percentage of patients satisfying the following QTcF conditions at any time postbaseline will be summarized:

- > 450, > 480, or > 500 msec;
- ≤ 30 msec maximum increase from baseline, > 30 and ≤ 60 msec maximum increase from baseline, or > 60 msec maximum increase from baseline.

A listing of abnormal ECG by patient and assessment timepoint will be generated.

6.5.6 ECOG Performance Status

ECOG performance status will be summarized by treatment arm at each assessment timepoint.

[redacted]

7 INTERIM ANALYSIS

There will be one interim analysis for the noninferiority (and superiority if noninferiority is met) testing of ORR. The interim analysis will be performed approximately 12 months after the randomization of 415 patients. The monitoring boundaries for the interim and the final analyses for the nonferiority and superiority tests are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending functions.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

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10. APPENDIX

APPENDIX A: IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will be imputed at the ADaM dataset level. The following rules will apply to the specific analysis and summary purposes mentioned below only. Date of death, discontinuation from study and analysis data cutoff will be accounted for in the date imputations as applicable.

A.1 Prior/Concomitant Medications/Procedures/Surgeries

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

A.2 Adverse Events

When the start date or end date of an AE is partially missing, the date will be imputed to determine whether the AE is treatment-emergent. When in doubt, the AE will be considered treatment-emergent by default. The following rules will be applied to impute partial dates for AEs:

If start date of an AE is partially missing, impute as follows:

- If both month and day are missing, then the imputed month and day will be January 01 or the date of first dose of study drug if they have the same year
- If only day is missing, then the imputed day will be the first day of the month or the date of first dose of study drug if they have the same month and year

- If the start date is completely missing, the imputed date will be the date of first dose of study drug as long as the AE end date is not before the date of first dose of study drug.

If the end date of an AE is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If the end date is completely missing, do not impute.

A.3 Deaths

For partial death dates, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01Jan or the last date the patient was known to be alive + 1, whichever is later
- If only day is missing, then the imputed day will be the first day of the month or the last date the patient was known to be alive +1, whichever is later

A.4 New Anti-cancer therapy

For partial dates of new anti-cancer therapies, dates will be imputed as for concomitant medication start dates.

A.5 Diagnosis

If a diagnosis date is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If a diagnosis date is completely missing, do not impute.

APPENDIX B: DERIVATION OF INVESTIGATOR DISEASE ASSESSMENT DATES

Dates corresponding to each investigator disease assessment (eg, CR, PR, PR-L) will be derived for disease assessments other than PD. Investigator assessments of PD will use the PD date provided directly by the investigator in the eCRF.

The investigator disease assessment is based on several individual assessments, eg, target and non-target lesions, liver/spleen and CBCs, and the disease assessment date derivation will be computed as the latest of the applicable individual assessments, which differ by investigator disease assessment and disease type (ie, CLL vs SLL) and are described in Table 3.

Table 3. Assessment Dates used for Investigator Disease Assessment Date Derivation

Assessment	Investigator Disease Assessment		
	CR, CRi	nPR	PR, PR-L, SD, NE
Target and non-target lesion imaging	Y	Y	Y
Liver / spleen imaging	Y	Y	Y
Physical exam of liver/spleen, lymph nodes	Y	Y	Y
CBC collection (CLL only)	Y	Y	Y
Bone marrow biopsy	N [1]	N [1]	N
Constitutional symptoms check (CLL only)	Y	Y	N

Y = assessment and corresponding date accounted for when determining investigator disease assessment date for given investigator disease assessment (eg, CR, PR); N = assessment not used for given investigator disease assessment. The latest of all dates with "Y" for the given investigator disease assessment will be the derived disease assessment date.

[1] bone marrow biopsy is relevant for certain disease assessments but will not be used to derive the assessment date.

APPENDIX C: DERIVATION OF BEST OVERALL RESPONSE FOR CLL

For CLL patients, the best overall response will require two assessments at least 8 weeks apart to confirm a best overall response of PR-L, PR, nPR, CRi or CR that meet the following criteria:

- To confirm a response of CR, there must be one CR and another CR or CRi in any order and can only have intervening responses of non-PD or NE and at most one intervening PR or nPR;

- To confirm a response of CRi, there must be two CRis and can only have intervening responses of non-PD or NE and at most one intervening PR or nPR;

- To confirm a response of nPR, confirmed CR or CRi must not be met and there must be EITHER an nPR with a subsequent nPR or higher OR an nPR or higher with a subsequent nPR, and can have intervening responses of PR-L, PR, non-PD, NE or SD;

- To confirm a response of PR, confirmed CR, CRi or nPR must not be met and there must be a PR or higher with a subsequent PR or higher and can have intervening responses of PR-L, non-PD, NE or SD;

- To confirm a response of PR-L, confirmed CR, CRi, nPR or PR must not be met and there must be a PR-L with a subsequent PR-L or higher or a PR-L or higher with a subsequent PR-L and can have intervening responses of non-PD, NE or SD;

- No other best overall response category requires confirmation.

Time to response will be the first PR or higher that is subsequently confirmed as a PR or higher.

For a sensitivity analysis of ORR with an alternative response confirmation, the best overall response will require two assessments at least 8 weeks apart to confirm a best overall response of PR-L, PR, nPR, CRi or CR that meet the following criteria:

- To confirm a response of CR, there must be one CR and another CR or CRi in any order and can only have intervening responses of non-PD or NE and at most one intervening PR or nPR;

- To confirm a response of CRi, there must be two CRis and can only have intervening responses of non-PD or NE and at most one intervening PR or nPR;

- To confirm a response of nPR, confirmed CR or CRi must not be met and there must be EITHER an nPR with a subsequent nPR or higher OR an nPR or higher with a subsequent nPR, and can have intervening responses of PR-L, PR, non-PD, NE or SD;

- To confirm a response of PR, confirmed CR, CRi or nPR must not be met and there must be a PR-L or higher with a subsequent PR or higher and can have intervening responses of PR-L, non-PD, NE or SD;

- To confirm a response of PR-L, confirmed CR, CRi, nPR or PR must not be met and there must be a PR-L or higher with a subsequent PR-L and can have intervening responses of non-PD, NE or SD;

- No other best overall response category requires confirmation.

For this sensitivity analysis, if a PR or higher is subsequently confirmed as PR or higher, then the date of first response will be the first PR or higher that is subsequently confirmed as a PR or higher, and if a PR-L is subsequently confirmed as PR, the date of first response will be the last PR-L or higher that is subsequently confirmed as a PR. If both scenarios apply, the date of first response will be the earlier of the two.

APPENDIX D: EORTC QLQ-C30 SCORING

The principle for scoring the QLQ-C30 applies to all scales/scores: raw scores are calculated as the average of the items that contribute to the scale.

A linear transformation to standardize the raw scores is utilized, so that the scores are ranged from 0 to 100. Increases in scores for functional domains (e.g., physical, role, social, emotional, etc.) are improvements while increases in scores for symptoms (e.g., fatigue, vomiting and nausea, diarrhea, pain, etc.) are deteriorations.

Missing Items

If at least half of the items for a scale are answered, then all the completed items are used to calculate the score. Otherwise, the scale score is set to missing.

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw Score

For all scores, the raw score (RS), is the mean of the component items

RS = $(I_1+I_2+\ldots+I_n)$/n

Derived Scale

The derived scales are obtained from the raw scores as defined in the EORTC manual. The derived scales have a more intuitive interpretation: larger function scale or global health status / QoL are improvements while larger symptom scales (e.g., pain, nausea, etc.) are deteriorations.

The derivation formulas are as follows:

Linear transformation

Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Scales of QLQ-C30

	Scale	Number of items	Item range	Item Numbers
Global health status/ QoL Global health status/QOL	QL2	2	6	29,30
Functional Scales				
Physical functioning	PF2	5	3	1, 2, 3, 4, 5
Role functioning	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21, 22, 23, 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom Scales/ items				
Fatigue	FA	3	3	10, 12, 18

Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial Difficulties	FI	1	3	28

EQ-5D-5L: for the 5 level Dimensions, scores on a 5-point Likert scale of 1 to 5, with level 1 indicating no problem and level 5 indicating extreme problems. The Health State is defined by combining one level from each dimension. Lower scores indicate better health.

VAS includes a scale of 0 to 100 with higher scores indicating better health status.

Scales of EQ-5D-5L

MOBILITY
I have no problems in walking about □
I have slight problems in walking about □
I have moderate problems in walking about □
I have severe problems in walking about □
I am unable to walk about □

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

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
PAIN / DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY / DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

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

YOUR HEALTH TODAY = ☐