NCT04551963

CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Drug–Drug Interaction Study of Zanubrutinib with Moderate and Strong CYP3A Inhibitors in Patients with B-Cell Malignancies
Protocol Identifier:	BGB-3111-113
Phase:	1
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	B-Cell Malignancies
Sponsor:	BeiGene Switzerland GmbH c/o Vischer AG Aeschenvorstadt 4 4051 Basel Switzerland
Reference Numbers:	United States IND 125326
Sponsor Medical Monitor	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol:	18 May 2020
Amendment 1:	06 October 2020
Amendment 2:	05 November 2020

[redacted]

FINAL PROTOCOL APPROVAL SHEET

A Drug-Drug Interaction Study of Zanubrutinib with Moderate and Strong CYP3A Inhibitors in Patients with B-Cell Malignancies

BeiGene Approval:

[redacted]

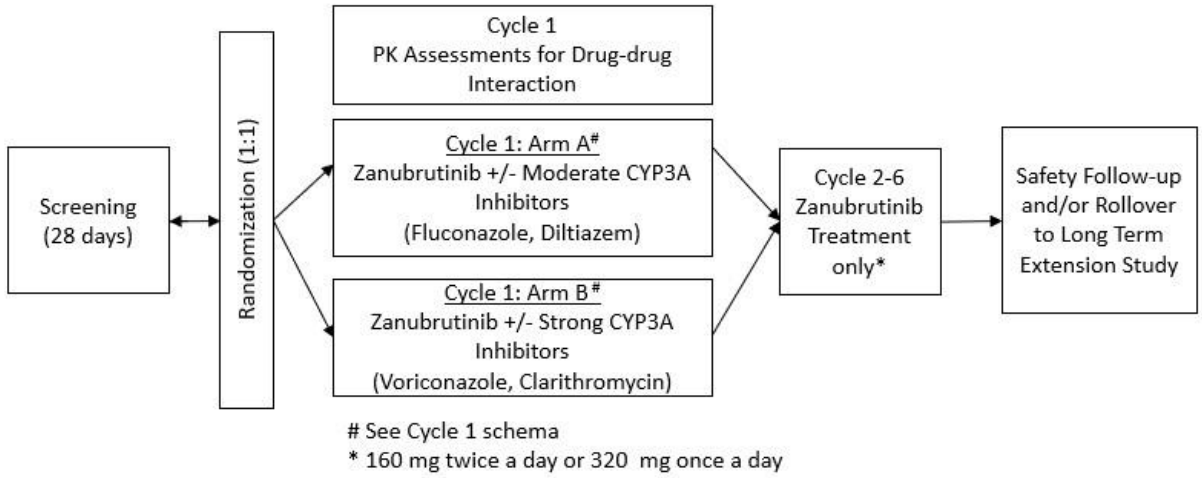
05 NOV 2020

Date

SYNOPSIS

Name of Sponsor/Company: BeiGene
Investigational Product: Zanubrutinib (BGB-3111)
Title of Study: A Drug–Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-Cell Malignancies
Protocol Identifier: BGB-3111-113
Phase of Development: 1
Number of Patients: Approximately 30
Study Centers: Approximately 6 to 8 sites
Study Objectives: The objective of the study is to assess the drug-drug interaction between zanubrutinib and moderate (fluconazole, diltiazem) and strong (voriconazole, clarithromycin) CYP3A inhibitors in patients with B-cell malignancies. **Primary:** • To assess the steady-state zanubrutinib pharmacokinetics (PK) when coadministered with moderate and strong CYP3A inhibitors. **Secondary:** • To evaluate the safety and tolerability of zanubrutinib alone, and when coadministered with moderate and strong CYP3A inhibitors. **Exploratory:** • To evaluate the efficacy of zanubrutinib.
Study Design This is a multicenter, Phase 1, open-label, randomized clinical drug-drug interaction study of zanubrutinib in approximately 30 patients with B-cell malignancies (15 in each Arm) to ensure that 24 subjects (12 in each Arm) complete the study. The study will include a PK study (Arm A and Arm B) in Cycle 1, as part of a Treatment Phase of six treatment cycles. Patients who continue to derive clinical benefit from zanubrutinib in the absence of unacceptable tolerability at the end of the Treatment Phase (6 cycles) will continue to receive zanubrutinib under a rollover extension study. Patients will be randomized to Arm A or Arm B to assess the effects of CYP3A inhibitors (fluconazole, diltiazem, voriconazole, clarithromycin) on PK of zanubrutinib in Cycle 1. Patients must not require chronic treatment with strong and moderate CYP3A inhibitors or inducers, including the inhibitors used in this study. Efficacy will be investigated during the subsequent treatment cycles and clinical safety will be investigated throughout the study. The overall study schematic and study schematic for the drug-drug interaction PK assessments are provided below.

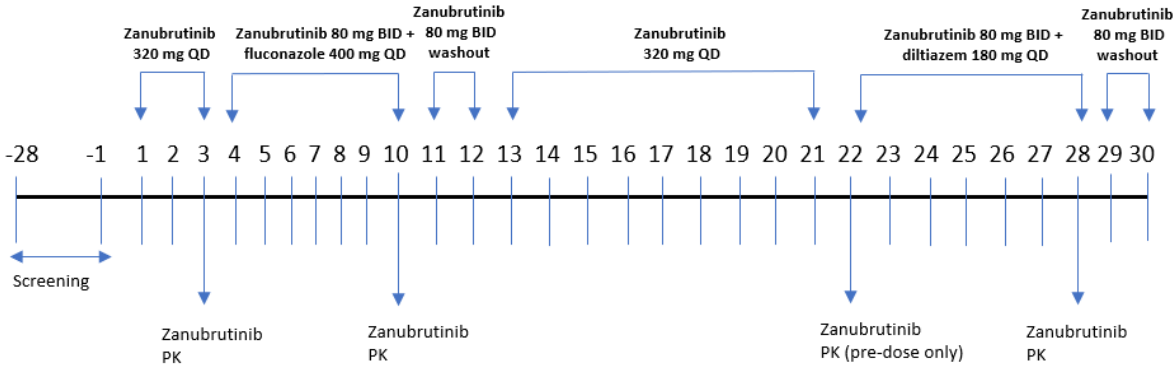
Study Schema



Abbreviation: PK, pharmacokinetic.

Study Schema for Drug-Drug Interaction Pharmacokinetic Assessment in Cycle 1

Arm A:



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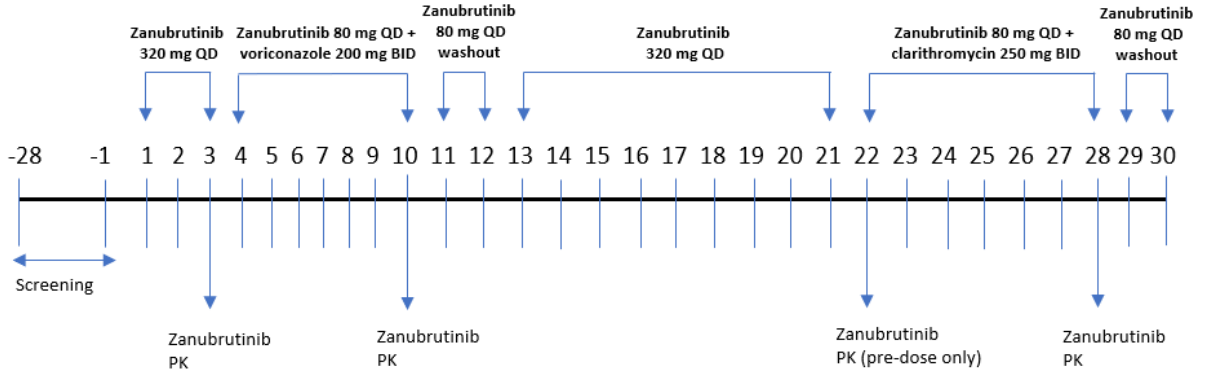

Abbreviations: BID, twice a day; PK, pharmacokinetic; QD, once a day.

Study elements

Inhibitors selection

Fluconazole, diltiazem, clarithromycin, and voriconazole will be used in this study. These CYP3A inhibitors were prescribed more often than others in zanubrutinib clinical studies and/or showed a wider degree of uncertainty based on physiologically-based pharmacokinetic modeling (PBPK) simulations for supporting the zanubrutinib label dose recommendation. Given that diltiazem and clarithromycin are both time-dependent inhibitors, these two drugs will be studied after administration of fluconazole and voriconazole in Arm A and Arm B, respectively.

Dose selection

Patients will receive zanubrutinib 320 mg once a day prior to administration of CYP3A inhibitors in Cycle 1 for steady-state zanubrutinib PK assessment. This allows for a wider exposure coverage for C_{max} (the 320 mg once a day dose has an approximately 2 times higher C_{max} than that of the 160 mg twice a day dose) in the presence of CYP3A inhibitor treatment. Zanubrutinib will be dosed at 80 mg twice a day and 80 mg once a day when coadministered with a moderate or strong CYP3A inhibitor in Arm A and Arm B, respectively.

After PK assessments in Cycle 1, patients will receive zanubrutinib 160 mg twice a day or 320 mg once a day from Cycle 2 to Cycle 6 (however, if patients' preference is 320 mg once a day, it is recommended that he/she continues to use the same dosing schedule throughout the 6 treatment cycles). Patients enrolled in the rollover extension study will receive 320 mg once a day.

Treatment Arms

Arm A

In Arm A, zanubrutinib will be administered with or without moderate CYP3A inhibitors. On PK sampling days (days 3 [alone], 10 [with fluconazole], and 28 [with diltiazem]), zanubrutinib is to be administered 30 min after a low-fat breakfast. On PK sampling days, the morning doses of fluconazole and diltiazem are to be administered together with zanubrutinib. On days where PK samples are not collected, zanubrutinib can be taken with or without food.

Zanubrutinib will be administered at 320 mg once a day from Day 1 to Day 3. Zanubrutinib PK will be assessed on Day 3. From Day 4 to Day 10, fluconazole will be administered once a day at a dose of 400 mg along with zanubrutinib at a reduced dose of 80 mg twice a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of fluconazole on Day 10 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 11 and Day 12, patients will receive zanubrutinib monotherapy 80 mg twice a day (to account for CYP3A inhibition that may continue after fluconazole treatment ends) followed by zanubrutinib 320 mg once a day from Day 13 to Day 21 to wash out potential effects of fluconazole.

A predose PK sample will be taken on Day 22. From Day 22 to Day 28, diltiazem will be administered once a day at a dose of 180 mg while patients receive zanubrutinib treatment at a reduced dose of 80 mg twice a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of diltiazem on Day 28 and will be compared to the zanubrutinib exposure

levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 29 and Day 30, patients will receive zanubrutinib monotherapy 80 mg twice a day (to account for CYP3A inhibition that may continue after diltiazem treatment ends).

Arm B

In Arm B, zanubrutinib will be administered with or without strong CYP3A inhibitors. On PK sampling days (Days 3 [alone], 10 [with voriconazole], and 28 [with clarithromycin], zanubrutinib is to be administered 30 minutes after a low-fat breakfast. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast. The morning dose of clarithromycin is to be administered together with zanubrutinib. On days where PK samples are not collected, zanubrutinib can be taken with or without food.

Zanubrutinib will be administered at 320 mg once a day from Day 1 to Day 3. Zanubrutinib PK will be assessed on Day 3. From Day 4 to Day 10, voriconazole will be administered twice a day at a dose of 200 mg (total daily dose of 400 mg), while patients receive zanubrutinib treatment at a reduced dose of 80 mg once a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of voriconazole on Day 10 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 11 and Day 12, patients will first receive zanubrutinib monotherapy 80 mg once a day (to account for CYP3A inhibition that may continue after voriconazole treatment ends) followed by 320 mg once a day from Day 13 to Day 21 to wash out potential effects of voriconazole.

A predose-only PK sample will be taken on Day 22. From Day 22 to Day 28, clarithromycin will be administered twice a day at a dose of 250 mg (total daily dose of 500 mg), while patients receive zanubrutinib treatment at a reduced dose of 80 mg once a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of clarithromycin on Day 28 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 29 and Day 30, patients will receive zanubrutinib monotherapy 80 mg once a day (to account for CYP3A inhibition that may continue after clarithromycin treatment ends).

Both Arms:

Patients in Arm A and Arm B will continue on zanubrutinib monotherapy (160 mg twice a day or 320 mg once a day) until disease progression, withdrawal of consent, death, lost to follow-up, discontinuation due to an adverse event, or end of study (completion of 6 cycles), whichever occurs first.

Efficacy assessments will occur during the subsequent treatment cycles, following the PK study; and clinical safety will be investigated throughout the study.

Patients who continue to derive clinical benefit from zanubrutinib in the presence of acceptable tolerability at the end of the Treatment Phase (6 cycles) will continue to receive zanubrutinib under a rollover extension study. Patients who discontinue treatment before 6 cycles will be followed post-treatment for survival in a rollover extension study.

Study Assessments:

Pharmacokinetic Assessments

Blood samples for measuring plasma zanubrutinib concentrations will be collected during

Cycle 1 on Day 3, Day 10, Day 22 (predose only) and Day 28 at the following timepoints: predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 hours postdose. Plasma samples will be analyzed using validated liquid chromatography coupled to tandem mass spectrometry methods.

Safety and Efficacy Assessments

Assessments of safety will include adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Adverse events will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. After informed consent has been signed, but prior to the administration of the study drug, only serious adverse events should be reported. After initiation of the study drugs, all adverse events and serious adverse events, regardless of relationship to study drugs, will be reported until 30 days after the last dose of study drugs. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment. An independent Data Monitoring Committee will periodically monitor safety data.

Overall response rate, rate of complete response or complete metabolic response, and time to response will be based on the investigator's assessment at the end of Cycles 3 and 6, using standard response criteria for each histologic subtype.

Key Eligibility Criteria

The patients to be included in this study will be 1) adults ≥ 18 years of age at the time of informed consent and with histologically or cytologically confirmed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), or marginal zone lymphoma (MZL). Patients will be required to have relapsed or refractory disease after at least 1 prior line of systemic therapy and a baseline Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients with MZL will be required to have failed an anti-CD20 monoclonal antibody-containing chemotherapy regimen.

Key exclusion criteria include requirement of chronic treatment with strong and moderate CYP3A inhibitors or inducers or with drugs that are not allowed to be used in combination with the CYP3A inhibitors in this study (ie, fluconazole, diltiazem, voriconazole, or clarithromycin); a history of stroke or intracranial hemorrhage (within 6 months of treatment start); known hypersensitivity or contraindication to zanubrutinib, diltiazem, fluconazole, clarithromycin, or voriconazole; prior exposure with zanubrutinib or other Bruton tyrosine kinase inhibitor; and any antitumor therapy within 3 weeks of initiating the study drug. Patients with moderate or severe hepatic impairment or moderate or severe renal impairment will not be eligible for the study.

Test Product, Dose, and Mode of Administration

Zanubrutinib will be administered at a 320 mg total daily dose using 80-mg capsules, or 80 mg twice a day (when used with a moderate CYP3A inhibitor), or 80 mg once a day (when used with a strong CYP3A inhibitor), 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.

On PK sampling days (Days 3 [alone], 10 [with fluconazole (Arm A) or voriconazole (Arm B)], and 28 [with diltiazem (Arm A) or clarithromycin (Arm B)]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. A predose-only PK sample will be taken on Day 22. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). The morning doses of fluconazole, diltiazem, and clarithromycin are to be administered together with zanubrutinib.

Patients may continue to receive zanubrutinib until disease progression, withdrawal of consent, death, lost to follow-up, discontinuation due to an adverse event, or end of study (completion of 6 cycles), whichever occurs first.

Reference Therapy, Dose, and Mode of Administration

For Arm A:

- fluconazole 400 mg once a day, given orally as 2 x 200-mg tablets, between Day 4 and Day 10.
- diltiazem 180 mg once a day, given orally as 1 x 180-mg extended release capsule, between Day 22 and Day 28.

For Arm B:

- voriconazole 200 mg twice a day, given orally as 2 x 200-mg tablets, between Day 4 and Day 10. Voriconazole tablets should be taken at least 1 hour before or at least 1 hour after meals. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast.
- clarithromycin 250 mg twice a day, given orally as 2 x 250-mg immediate release tablets, between Day 22 and Day 28.

Primary Endpoint:

- The primary endpoint assesses PK parameters including $AUC_{0\text{-}t}$, AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$), C_{max}, time to reach the C_{max} (T_{max}), and apparent terminal elimination half-life ($t_{1/2}$) as determined by blood samples collection during Cycle 1 on Day 3, Day 10, and Day 28.

Secondary Endpoints:

- Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs.

Exploratory Endpoints:

- Overall response rate, defined as the proportion of patients who achieve a partial response or higher for MCL and MZL patients, and partial response with lymphocytosis for CLL/SLL patients. For WM patients, overall response rate is defined as the proportion of patients achieving complete response, very good partial response, partial response, or minor response.
- Rate of complete response or complete metabolic response, defined as the proportion of patients who achieve a complete response or complete metabolic response.
- Time to response, defined as time from randomization to the first documentation of response.

Statistical Methods:

Primary PK Analysis:

The following PK parameters will be assessed for zanubrutinib: C_{max}, time to reach the C_{max} (T_{max}), area under plasma concentration-time curve (AUC) from 0 to the time of the last quantifiable concentration, AUC from 0 to 24 hours ($AUC_{0–24h}$), and apparent terminal elimination half-life on Day 3 in the absence of CYP3A inhibitors and on Day 10 and Day 28 in the presence of CYP3A inhibitors. Additional PK parameters may be calculated as needed.

PK analyses will be performed by standard non-compartmental analysis methods using Phoenix® WinNonlin™ version 7.0 or higher (Certara USA, Inc., Princeton, New Jersey). The PK evaluable analysis set will include all patients who received at least 1 dose of zanubrutinib and have evaluable PK data (at least 1 PK parameter can be calculated). A patient may be excluded from the PK summary statistics and statistical analysis if the patient has an adverse event of vomiting that occurs at or before 2 times the median T_{max} of zanubrutinib. The geometric mean ratios of PK parameters of zanubrutinib with and without coadministration of the CYP3A inhibitors and the associated 90% confidence interval will be constructed based on the least squares means) and intrapatient coefficient of variation from a mixed effects model of log-transformed PK parameters.

Safety Analysis:

The Safety Analysis Set will include all patients who received at least 1 dose of zanubrutinib. All summaries of the safety data will be provided for each arm and for the pooled arms based on the Safety Analysis Set.

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

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities terms and graded according to the NCI-CTCAE v5.0. All treatment-emergent adverse events will be summarized. A treatment-emergent adverse event is defined as an adverse event that had an onset date on or after the first dose of study drug up to 30 days after the last treatment with zanubrutinib or was worsening in severity from baseline (pretreatment) but before the date of starting any new anticancer therapy, whichever occurs first.

Treatment-emergent adverse events of any grade, serious adverse events, treatment-emergent adverse events ≥ Grade 3, treatment-emergent adverse events leading to treatment discontinuation, dose reduction, dose interruption, death, and treatment-related adverse events will be summarized. Treatment-emergent adverse events will also be summarized by system organ class, preferred term, and worst grade. A patient will be counted only once by the highest severity grade within a system organ class and preferred term, even if the patient experienced more than 1 treatment-emergent adverse event within a specific system organ class and preferred term. Treatment-related adverse events include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. Incidence and time to selected treatment-emergent adverse events of special interest will also be summarized.

The number of deaths and the cause of death will also be summarized.

Clinical laboratory data with values outside of the normal ranges will be identified. Selected laboratory data will be summarized by grade. Change from baseline to the worst postbaseline grade will be summarized. Vital signs will be summarized by visit.

Exploratory Analysis for Efficacy:

Summaries of efficacy will be provided separately for each histologic subtype, and for pooled subtypes. Overall response rate, rate of complete response or complete metabolic response, and time to response based on the investigator's assessment using standard response criteria for each histologic subtype will be analyzed for the Safety Analysis Set.

- Overall response rate will be estimated as the proportion of patients who achieve partial response or higher for MCL and MZL patients, and partial response with lymphocytosis for CLL/SLL patients. For WM patients, overall response rate is defined as the proportion of patients achieving complete response, very good partial response, partial response, or minor response. A 2-sided 95% exact binomial confidence interval for overall response rate will be provided.
- Rate of complete response or complete metabolic response will be analyzed using the same methods employed for overall response rate.
- Time to response will be summarized by sample statistics such as mean, median, and standard deviation for responders only.

Sample Size Considerations

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations. Approximately 30 patients with B-cell malignancies (15 in each arm) will be enrolled to ensure that 24 patients (12 in each arm) complete the study.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AUC	area under plasma concentration-time curve
ANC	absolute neutrophil count
BTK	Bruton tyrosine kinase
C_{max}	time to maximum plasma concentration
CLL	chronic lymphocytic leukaemia
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IRB	Institutional Review Board
MCL	mantle cell lymphoma
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCR	polymerase chain reaction
PD	progressive disease
PK	pharmacokinetic
SLL	small lymphocytic lymphoma
WM	Waldenström macroglobulinemia
zanubrutinib	BGB-3111

1. INTRODUCTION

Inhibition of Bruton tyrosine kinase (BTK) has emerged as a promising strategy for the treatment of B-cell malignancies. BTK, a member of the transient erythroblastopenia of childhood family kinases, is a critical component of the B-cell receptor signaling cascade. Zanubrutinib (BRUKINSA™; also known as BGB-3111), a BTK inhibitor, has been granted an accelerated approval by the US Food and Drug Administration on 14 November 2019 for the indication of treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy.

Zanubrutinib is a novel, second-generation, small molecule oral inhibitor of BTK that works by forming an irreversible covalent bond at Cys_{481} within the adenosine triphosphate binding pocket of BTK. Zanubrutinib has been shown to be more selective than ibrutinib, an approved agent, for inhibition of BTK against off-target kinases, including EGFR, JAK3, HER2, TEC, inducible tyrosine kinase, and others based on results from kinase inhibition and cell-based assays. The increased selectivity of zanubrutinib for BTK may result in a lower incidence and severity of off-target toxicities linked to inhibition of the aforementioned kinases. Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced, antibody-dependent cell-mediated cytotoxicity, consistent with its more selective activity against BTK and weaker inducible tyrosine kinase inhibitory activity than ibrutinib, as revealed in both biochemical and cellular assays.

Zanubrutinib is being developed by BeiGene as a second-generation inhibitor of BTK for the treatment of B-cell malignancies, including MCL, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), follicular lymphoma, marginal zone lymphoma (MZL), and diffuse large B-cell lymphoma, as a monotherapy and/or in combination with other agents. Zanubrutinib entered global clinical development in August 2014 and is being investigated in ongoing Phase 1, 2, and 3 studies in patients with B-cell malignancies (Zanubrutinib Investigator's Brochure, 2020).

Zanubrutinib was rapidly absorbed and eliminated after oral administration in humans. The peak concentrations occurred around 2 hours postdose and the mean apparent terminal elimination half-life ($t_{½}$) was approximately 2 to 4 hours. The time to maximum plasma concentration (C_{max}) and the drug exposure (the area under the curve [AUC]) increased in a nearly dose proportional manner from 40 mg to 320 mg, both after the single-dose and repeat-dose administrations.

A human absorption, metabolism, excretion study indicated that zanubrutinib was primarily eliminated by hepatic metabolism and fecal excretion. Approximately 87.1% of the radiolabeled dose was excreted in feces with only 0.4% of the dose excreted in urine as parent drug. CYP3A isoenzymes are the principal metabolic pathway for zanubrutinib.

Anticancer agents are often concomitantly prescribed with antibacterial and/or antifungal agents, some of which are known CYP3A inhibitors. Of those, clarithromycin, fluconazole, and voriconazole are approved therapeutic agents in multiple countries and were prescribed more often than others in the treatment of bacterial and fungal infections in zanubrutinib clinical studies. Fluconazole is a moderate CYP3A and CYP2C9 inhibitor, clarithromycin is a strong CYP3A inhibitor, while voriconazole is a strong CYP3A inhibitor and a moderate and weak inhibitor of the CYP2C19 and CYP2C9 enzymes, respectively (FDA 2019). Furthermore, the majority of patients with B-cell malignancies are elderly with comorbidities requiring

medications. Use of comedications such as a calcium channel blockers (eg, diltiazem to treat hypertension) can inhibit CYP3A activity and potentially impact exposure of zanubrutinib.

A drug-drug interaction (DDI) study has been conducted to assess the potential impact of CYP3A modulator on the exposure of zanubrutinib in healthy volunteers (BGB-3111-104). The results indicated that coadministration of zanubrutinib with strong CYP3A inhibitor itraconazole (200 mg once a day for 4 days) increased exposure of zanubrutinib by 3.8-fold for AUC from 0 to infinity 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 physiologically based pharmacokinetic model was developed and was used to predict the effect of moderate CYP3A inhibitors and CYP3A inducers on the pharmacokinetics (PK) of zanubrutinib. Physiologically based pharmacokinetic simulations suggest that coadministration of multiple doses of a moderate CYP3A inhibitor (eg, fluconazole, diltiazem) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. Thus, it was recommended a zanubrutinib dose reduction to 80 mg once a day when zanubrutinib is coadministered with a strong CYP3A inhibitor and to 80 mg twice a day when coadministered with a moderate CYP3A inhibitor.

In this Phase 1 study, zanubrutinib will be coadministered with moderate (diltiazem, fluconazole) and strong (clarithromycin, voriconazole) CYP3A inhibitors in patients with B-cell malignancies to confirm the magnitude of zanubrutinib's DDI when used concomitantly with moderate or strong CYP3A inhibitors and to evaluate dose adjustment recommendations.

1.1. Zanubrutinib (BGB-3111)

1.1.1. Summary of Relevant Clinical Experience with Zanubrutinib

1.1.1.1. Dose Selection for Zanubrutinib

Patients will receive 320 mg once a day prior to administration of CYP3A inhibitors in Cycle 1 for steady-state zanubrutinib PK assessment. This allows for wider exposure coverage for C_{max} (320 mg once a day dose has approximately 2 times higher C_{max} than that of the 160 mg twice a day dose) in the presence of inhibitor treatment. Selection of zanubrutinib 80 mg twice a day or 80 mg once a day when coadministered with moderate and strong CYP3A inhibitors, respectively, is based on results of a clinical DDI study (BGB-3111-104) and physiologically based pharmacokinetic simulations. After the PK assessment in Cycle 1, patients will receive 160 mg twice a day or 320 mg once a day from Cycle 2 to Cycle 6.

A total daily dose of 320 mg (160 mg orally twice a day or 320 mg orally once a day) is the recently approved dose for adult patients with MCL who have received at least 1 prior therapy (BRUKINSA 2019). Selection of this dose was based on results from the Phase 1 dose-finding Study BGB-3111-AU-003, which evaluated the pharmacokinetics/pharmacodynamics, safety, and efficacy of zanubrutinib at doses from 40 mg to 320 mg once a day and 160 mg twice a day. A maximum tolerated dose was not reached in Study BGB-3111-AU-003, and no dose-limiting toxicity was observed during the dose escalation part of the study (Zanubrutinib Investigator's Brochure, 2020). In addition, nearly full BTK occupancy in peripheral blood mononuclear cells was observed at steady-state trough concentrations at all doses. Additionally, in the 160 mg twice a day and 320 mg once a day dose groups, median steady state BTK occupancy was 100% and 94% in lymph node tissue, respectively

(Tam et al 2015). Available clinical efficacy/safety data and the exposure-response analysis indicate no evidence of differences in clinical efficacy/safety profiles between the 320 mg once a day and 160 mg twice a day dose regimens.

1.1.1.2. Additional Data on Clinical Pharmacology of Zanubrutinib

Results from a food effect study (BGB-3111-103) showed that dosing with food (high-fat or low-fat meal) did not cause any significantly meaningful effects on the AUC of zanubrutinib, therefore, zanubrutinib can be administered with or without food.

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.

A dedicated hepatic impairment study (BGB-3111-107) showed that there was no substantial difference in PK between patients with mild/moderate hepatic impairment and healthy subjects. An approximately 60% increase in AUC was observed in patients with severe hepatic impairment, which is within the range of PK variability that has been observed for zanubrutinib.

A clinical DDI study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), and BCRP (rosuvastatin) using a cocktail approach. The results showed that zanubrutinib does not affect drugs metabolized by CYP2C9 (warfarin) or transported by BCRP (statins). Zanubrutinib had a weak induction effect on CYP3A and CYP2C19 enzymes. The AUC from 0 to the time of the last quantifiable concentration (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. Benefit-Risk Assessment

Cumulatively, as of 31 August 2019, over 1500 patients have been enrolled worldwide in completed and ongoing clinical studies evaluating zanubrutinib and have received at least 1 dose of zanubrutinib. Zanubrutinib was highly active in multiple B-cell malignancies including MCL, CLL/SLL, WM, follicular lymphoma, MZL, and diffuse large B-cell lymphoma. For more detailed information on the clinical experience for zanubrutinib, please refer to the Investigator's Brochure (Zanubrutinib Investigator's Brochure, 2020).

2. STUDY OBJECTIVES

The objective of this study is to assess DDI between zanubrutinib and moderate (diltiazem, fluconazole) and strong (clarithromycin, voriconazole) CYP3A inhibitors in patients with B-cell malignancies.

Primary:

- To assess the steady-state zanubrutinib PK when coadministered with moderate and strong CYP3A inhibitors.

Secondary:

- To evaluate the safety and tolerability of zanubrutinib alone and when coadministered with moderate and strong CYP3A inhibitors.

Exploratory:

- To evaluate efficacy of zanubrutinib.

3. STUDY DESIGN

3.1. Rationale of Study

A DDI study in healthy volunteers has showed that CYP3A inhibitors can significantly impact the exposure of zanubrutinib (BGB-3111-104). This study assesses the DDI between zanubrutinib and 4 additional moderate or strong CYP3A inhibitors in patients with B-cell malignancies.

3.2. Summary of Study Design

This is a multicenter, Phase 1, open-label, randomized clinical DDI study of zanubrutinib in approximately 30 patients with B-cell malignancies (15 in each arm) to ensure that 24 patients (12 in each arm) complete the study. The study will include a PK study (Arm A and Arm B) in Cycle 1 as part of a Treatment Phase of 6 treatment cycles (30 days in Cycle 1 and 28 days in Cycles 2 to 6). Patients who continue to derive clinical benefit from zanubrutinib in the absence of unacceptable tolerability at the end of the Treatment Phase (6 cycles) will continue to receive zanubrutinib under a rollover extension study. Patients who discontinue treatment before 6 cycles will be followed post-treatment for survival in a rollover extension study.

Patients will be randomized to Arm A or Arm B to assess the effects of CYP3A inhibitors (fluconazole, diltiazem, voriconazole, clarithromycin) on PK of zanubrutinib in Cycle 1 (Figure 2). Patients must not require chronic treatment with strong and moderate CYP3A inhibitors or inducers, including the inhibitors used in this study. Efficacy will be investigated during the subsequent treatment cycles, and clinical safety will be investigated throughout the study.

3.2.1. Study Assessments:

3.2.1.1. Pharmacokinetic Assessments

Blood samples for measuring plasma zanubrutinib concentrations will be collected during Cycle 1 on Day 3, Day 10, Day 22 (predose only) and Day 28 at the following timepoints: predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 hours postdose (Appendix 5). Plasma samples will be analyzed using validated liquid chromatography coupled to tandem mass spectrometry methods.

3.2.1.2. Safety and Efficacy Assessments

Assessments of safety will include adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Adverse events will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. After informed consent has been signed, but prior to the administration of the study drug, only serious adverse events should be reported. After initiation of the study drugs, all adverse events and serious adverse events, regardless of relationship to study drugs, will be reported until 30 days after the last dose of study drugs. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment. An independent Data Monitoring Committee will periodically monitor safety data.

Overall response rate, rate of complete response (CR) or complete metabolic response, and time to response will be based on the investigator's assessment using standard response criteria for each histologic subtype.

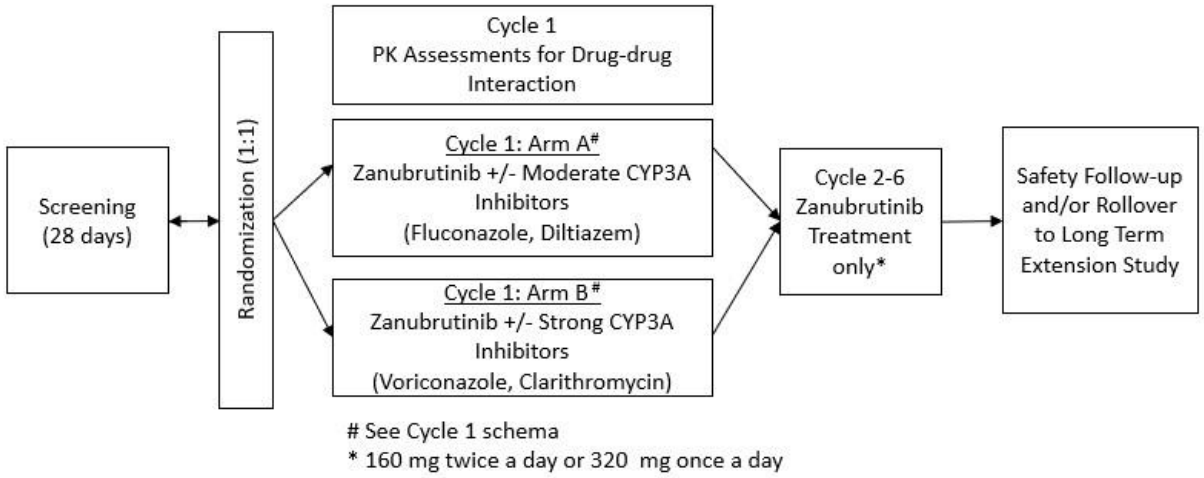
3.2.2. Blinding

Not applicable. Treatment with zanubrutinib and moderate or strong CYP3A inhibitors will be open label.

3.3. Study Schema

The overall study schematic is provided in Figure 1. Study schematic for DDI PK assessments in Cycle 1 is provided in Figure 2.

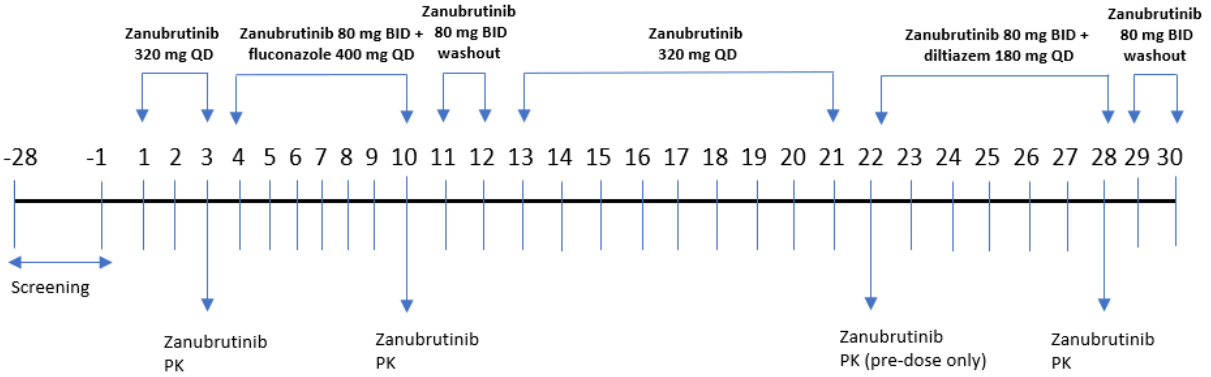
Figure 1: Study Schema



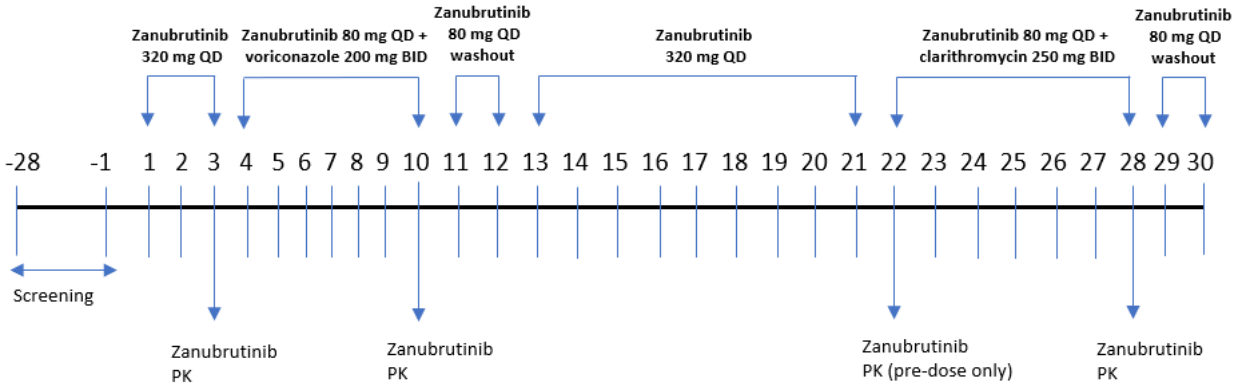
Abbreviation: PK, pharmacokinetic.

Figure 2: Study Schema for Drug-Drug Interactions Pharmacokinetic Assessments in Cycle 1

Arm A:



Arm B:



Abbreviations: BID, twice a day; PK, pharmacokinetic; QD, once a day.

3.4. Duration of Study

This study will include a PK study (Arm A and Arm B) in Cycle 1 (30 days) as part of a Treatment Phase of 6 treatment cycles (Cycles 2 to 6, 28-day cycles).

3.5. Study Design Rationale

Treatment Arms

Arm A

In Arm A, zanubrutinib will be administered with or without moderate CYP3A inhibitors. On PK sampling days (Days 3 [alone], 10 [with fluconazole], and 28 [with diltiazem]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. A predose-only PK sample will be taken on Day 22. On PK sampling days, the morning doses of fluconazole and diltiazem are to

be administered together with zanubrutinib. On days where PK samples are not collected, zanubrutinib can be taken with or without food (FDA 2019).

Zanubrutinib will be administered at 320 mg once a day from Day 1 to Day 3. Zanubrutinib PK will be assessed on Day 3. From Day 4 to Day 10, fluconazole will be administered once a day at a dose of 400 mg along with zanubrutinib at a reduced dose of 80 mg twice a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of fluconazole on Day 10 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 11 and Day 12, patients will receive zanubrutinib monotherapy 80 mg twice a day (to account for CYP3A inhibition that may continue after fluconazole treatment ends) followed by zanubrutinib 320 mg once a day from Day 13 to Day 21 to wash out potential effects of fluconazole.

From Day 22 to Day 28, diltiazem will be administered once a day at a dose of 180 mg while patients receive zanubrutinib treatment at a reduced dose of 80 mg twice a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of diltiazem on Day 28 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 29 and Day 30, patients will receive zanubrutinib monotherapy 80 mg twice a day (to account for CYP3A inhibition that may continue after diltiazem treatment ends).

Arm B

In Arm B, zanubrutinib will be administered with or without strong CYP3A inhibitors. On PK sampling days (Days 3 [alone], 10 [with voriconazole], and 28 [with clarithromycin]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. A predose-only PK sample will be taken on Day 22. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). The morning dose of clarithromycin is to be administered together with zanubrutinib. On days where PK samples are not collected, zanubrutinib can be taken with or without food (FDA 2019).

Zanubrutinib will be administered at 320 mg once a day from Day 1 to Day 3. Zanubrutinib PK will be assessed on Day 3. From Day 4 to Day 10, voriconazole will be administered twice a day at a dose of 200 mg (total daily dose of 400 mg) while patients receive zanubrutinib treatment at a reduced dose of 80 mg once a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of voriconazole on Day 10 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 11 and Day 12, patients will first receive zanubrutinib monotherapy 80 mg once a day (to account for CYP3A inhibition that may continue after voriconazole treatment ends) followed by 320 mg once a day from Day 13 to Day 21 to wash out potential effects of voriconazole.

From Day 22 to Day 28, clarithromycin will be administered twice a day at a dose of 250 mg (total daily dose of 500 mg) while patients receive zanubrutinib treatment at a reduced dose of 80 mg once a day. Steady-state zanubrutinib PK will be assessed after repeated dosing of clarithromycin on Day 28 and will be compared to the zanubrutinib exposure levels on Day 3 in the absence of CYP3A inhibitor treatment. On Day 29 and Day 30, patients will receive zanubrutinib monotherapy 80 mg once a day (to account for CYP3A inhibition that may continue after clarithromycin treatment ends).

Both Arms

Patients in Arm A and Arm B will continue on zanubrutinib monotherapy (160 mg twice a day or 320 mg once a day) until disease progression, withdrawal of consent, death, lost to follow-up, discontinuation due to an adverse event, or end of study (completion of 6 cycles), whichever occurs first.

Efficacy assessments will occur during the subsequent treatment cycles, following the PK study, and clinical safety will be investigated throughout the study.

Patients who continue to derive clinical benefit from zanubrutinib in the presence of acceptable tolerability at the end of the Treatment Phase (6 cycles) will continue to receive zanubrutinib under a rollover extension study. Patients who discontinue treatment before 6 cycles will be followed post-treatment for survival in a rollover extension study.

3.5.1. Inhibitor Selection

Fluconazole, diltiazem, clarithromycin, and voriconazole will be used in this study. These CYP3A inhibitors were prescribed more often than others in zanubrutinib clinical studies and/or showed wider degree of uncertainty based on physiologically based pharmacokinetic modeling simulations for supporting the label dose recommendation. Given that diltiazem and clarithromycin are both time-dependent inhibitors, these 2 drugs will be studied after administration of fluconazole and voriconazole in Arm A and Arm B, respectively (Albaugh et al, 2012; Chen et al, 2011).

3.5.2. Dose Selection

Patients will receive zanubrutinib 320 mg once a day prior to administration of CYP3A inhibitors in Cycle 1 for steady-state zanubrutinib PK assessment. This allows for a wider exposure coverage for C_{max} (the 320 mg once a day dose has an approximately 2 times higher C_{max} than that of the 160 mg twice a day dose) in the presence of CYP3A inhibitor treatment. Zanubrutinib will be dosed at 80 mg twice a day and 80 mg once a day when coadministered with a moderate or strong CYP3A inhibitor in Arm A and Arm B, respectively.

After PK assessment in Cycle 1, patients will receive zanubrutinib 160 mg twice a day or 320 mg once a day from Cycle 2 to Cycle 6 (however, if patients' preference is 320 mg once a day, it is recommended that he/she continues to use the same dosing schedule throughout the 6 treatment cycles). The same dose will be administered. Patients enrolled in the rollover extension study will receive zanubrutinib 320 mg once a day.

4. SELECTION OF STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Adults ≥ 18 years of age at the time of informed consent.
2. Histologically or cytologically confirmed CLL/SLL, MCL, WM, or MZL. Patients will be required to have relapsed or refractory disease after at least 1 prior line of systemic therapy. Patients with WM must meet at least 1 criterion for treatment according to consensus panel criteria from the Seventh International Workshop on WM (Appendix 7). Patients with MZL will be required to have failed an anti-CD20 monoclonal antibody-containing chemotherapy regimen.
3. Baseline Eastern Cooperative Oncology Group performance status of 0 to 1.
4. Adequate bone marrow function defined as:
   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. the screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of pegfilgrastim and at least 7 days following the most recent administration of other myeloid growth factors (eg, G-CSF, GM-CSF)
   c. Platelet count ≥ 50,000/mm^3, independent of growth factor support or transfusion within 7 days of study entry
   d. Hemoglobin ≥ 7.5 g/dL (may be post-transfusion).
5. Creatinine clearance of ≥ 50 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate from the Modification of Diet in Renal Disease) based on ideal body mass, or as measured by nuclear medicine scan or 24-hour urine collection.
6. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase and alanine aminotransferase/serum glutamic-pyruvic transaminase ≤ 1.5 x upper limit of normal.
7. Total bilirubin level ≤ 2 x upper limit of normal (unless documented Gilbert's syndrome).
8. International normalized ratio ≤ 1.5 x upper limit of normal and activated partial thromboplastin time ≤ 1.5 x upper limit of normal.

9. Female patients of childbearing potential and non-sterile males must practice highly effective methods of birth control initiated before the first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib. These methods include the following:

a. Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation.

    i. Oral, intravaginal, or transdermal

b. Progestogen-only hormonal contraception associated with the inhibition of ovulation

    ii. Oral, injectable, or implantable

c. Intrauterine device.
d. Intrauterine hormone-releasing system.
e. Bilateral tubal occlusion.
f. 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).
g. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug, starting the day before first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib). 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 study drug, and withdrawal are not acceptable methods of contraception.

    i. 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.

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

    iii. 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 high follicle stimulating hormone measurement is insufficient.

h. Male patients are eligible if abstinent (as defined above), vasectomized or if they agree to the use of barrier contraception in combination with other methods described above during the study drug period and for ≥ 90 days after the last dose of zanubrutinib.

10. Patients who relapse after autologous stem cell transplant are eligible 3 months after transplant, and patients who relapse after allogeneic transplant are eligible 6 months after transplant. To be eligible after either type of transplant, patients should have no active infections or, in the case of allogeneic transplant relapse, no active acute graft versus host disease of any grade, and no chronic graft versus host disease other than mild skin, oral, or ocular graft versus host disease not requiring systemic immunosuppression.

4.2. Exclusion Criteria

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

1. Known hypersensitivity or contraindication to zanubrutinib, diltiazem, fluconazole, clarithromycin, or voriconazole.
2. Prior exposure to zanubrutinib or other BTK inhibitors.
3. Requirement of chronic treatment with strong and moderate CYP3A inhibitors or inducers or with drugs that are not allowed to be used in combination with diltiazem, clarithromycin, fluconazole, or voriconazole.
4. History of stroke or intracranial hemorrhage (within 6 months of treatment start).
5. Any antitumor therapy given within 3 weeks of initiating study drug.
6. Patients with moderate or severe hepatic impairment, ie, Child-Pugh class B or C.
7. Evidence of disease transformation at the time of study entry.
8. Ongoing requirement for systemic corticosteroid other than systemic adrenal replacement therapy.
9. Major surgery within 4 weeks of study drug.
10. 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 4).
11. Prior or concurrent active malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer.
12. Clinically significant cardiovascular disease including the following:

a. Myocardial infarction within 6 months before screening.
b. Unstable angina within 3 months before screening.
c. New York Heart Association class III or IV congestive heart failure (see Appendix 12).
d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes).
e. QTcF > 480 msecs based on Fredericia'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.

13. History of sinus bradycardia, low blood pressure or orthostatic hypotension.
14. Unable to comply with study medication requirements including taking zanubrutinib and inhibitors on schedule every day, and consumption of grapefruit or grapefruit juice during Cycle 1.
15. 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.
16. Active fungal, bacterial and/or viral infection requiring systemic therapy.
17. Known infection with HIV, or serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) 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 HBV DNA is undetectable (< 20 IU), and if they are willing to undergo monthly monitoring for HBV reactivation.
b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (<15 IU/mL).

18. Pregnant or lactating women.
19. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events.
20. Vaccination with a live vaccine within 35 days prior to the first dose of study drug.
21. Ongoing alcohol or drug addiction.
22. 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.
23. Concurrent participation in another therapeutic clinical study.
24. Known central nervous system involvement by leukemia or lymphoma.
25. Patient has used or ingested a strong or moderate inducer (eg, St John's wort) or a strong/moderate inhibitor (eg, itraconazole) of cytochrome P450 3A4 within 14 days prior to study drug dosing.

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 2, Appendix 3, Appendix 4 and Appendix 5).

5.1. Visit Windows

A study visit in Cycle 1 must occur on the exact date indicated. From Day 1 of Cycle 2, study visits may be scheduled on any day within a specified study week (7-day period).

5.2. Informed Consent

At the Screening Visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the Informed Consent Form (ICF) will be given to the patient to read and the patient must have adequate time to digest and ask questions.

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 28-day Screening Period. Consent must be obtained using the most current version of the form approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).

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

For patients who provide informed consent and subsequently do not meet eligibility criteria, 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.

5.3. Screening

All screening procedures must be performed up to 28 days before the first administration of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. The site investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

5.3.1. 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 starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

5.3.2. Medical and Cancer History

Medical and cancer history will be reviewed any time after obtaining informed consent during screening. Clinically significant medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the patient's study eligibility will be collected and captured in the electronic case report form (eCRF). "Clinically significant" is defined as any events, diagnoses or laboratory values requiring treatment, follow-up, or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Prior medications/significant non-drug therapies and demographic data (gender, year of birth [or age] and race/ethnicity) will also be collected.

Information will also be collected regarding childbearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, and ECG). For further details on eligibility assessments, please see Appendix 2, Appendix 3 and Appendix 4 .

5.3.3. Confirmation of Eligibility

The investigator is responsible for ensuring that the patient meets the eligibility criteria for this study. An eligibility packet that contains a checklist of the inclusion/exclusion criteria and scanned copies of patient's source data/documents will need to be provided to the medical monitor or designee for review during the Screening Period. Medical monitor or designee will confirm whether the patient is eligible for the study and confirmation will be sent to the site. The patient cannot be started on study drug until confirmation from the medical monitor or designee is received.

5.3.4. Enrollment/Randomization

After a patient has been approved by the medical monitor or designee to enroll in the study, study center personnel can enroll the patient in the Interactive Response Technology system to manage study drug. Study site personnel should ensure that a medical monitor approved Eligibility Authorization Packet is in the patient's file before proceeding with randomization. Study drug must commence within 5 days after randomization/treatment assignment.

5.4. Zanubrutinib Dispensation

During Cycle 1, zanubrutinib will be administered at 320 mg once a day using 80-mg capsules, or 80 mg twice a day (when used with moderate CYP3A inhibitor), or 80 mg once a day (when used with strong CYP3A inhibitor), with or without food. Beginning on Cycle 2 Day 1, zanubrutinib will be administered at 160 mg twice a day or 320 mg once a day. Patients enrolled in the rollover extension study will receive zanubrutinib 320 mg once a day. 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.

On PK sampling days (Days 3 [alone], 10 [with fluconazole (Arm A) or voriconazole (Arm B)], and 28 [with diltiazem (Arm A) or clarithromycin (Arm B)]), zanubrutinib is to be administered

30 minutes after a low-fat breakfast. A predose-only PK sample will be taken on Day 22. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). The morning doses of fluconazole, diltiazem, and clarithromycin are to be administered together with zanubrutinib.

Patients may continue to receive zanubrutinib until disease progression, withdrawal of consent, death, lost to follow-up, discontinuation due to an adverse event, or end of study (completion of 6 cycles), whichever occurs first. Patients who continue to derive clinical benefit from zanubrutinib in the presence of acceptable tolerability at the end of the Treatment Phase (6 cycles) will continue to receive zanubrutinib under a rollover extension study.

Zanubrutinib bottles will be assigned through the Interactive Response Technology system and dispensed by the study center personnel to patients at scheduled study visits, to ensure adequate drug supply for administration at home throughout the Treatment Phase. Center personnel should ensure that the bottle number(s) assigned by the Interactive Response Technology system correspond to the bottles being handed to the patient. Instructions are to be provided to patients for dosing, storage, and the return of all bottles (used and unused) at future visits. Drug accountability should be performed at each visit.

5.5. Pharmacokinetics

Blood will be collected to characterize the PK of zanubrutinib. The timing of blood sampling procedures is provided in Appendix 5.

Blood samples for measuring plasma zanubrutinib concentrations will be collected during Cycle 1 on Day 3, Day 10, Day 22 (predose only), and Day 28 at the following timepoints: predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 hours postdose (given that zanubrutinib has a half-life of 2 to 4 hours and reaches steady-state within 24 hours, concentrations at predose sample on the planned collection days can be used to estimate concentrations at 24 hours postdose). The actual dosing time will be collected, including dosing time of the evening dose (for the twice a day dose) prior to PK sampling on the next day.

The actual time each sample is collected will be captured to the nearest minute in the eCRF and recorded in the database.

Blood samples for PK analysis will be collected into ethylenediaminetetraacetic acid collection tubes. Details concerning handling of the PK plasma samples, including labeling and shipping instructions, will be provided in the Laboratory Manual for this study. Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma zanubrutinib concentrations using a validated liquid chromatography coupled to tandem mass spectrometry methods.

5.6. Safety Assessments

5.6.1. Physical Examination and Vital Signs

Physical examination including vital signs (sitting blood pressure, pulse rate, and body temperature), weight, constitutional symptoms, and signs and symptoms of ventricular arrhythmia (eg, shortness of breath, dizziness, or fainting) assessments will be performed at the

timepoints specified (See Appendix 2, Appendix 3, and Appendix 4). These signs and symptoms will be monitored throughout the study at every visit. Height (cm) is measured at screening only.

Body systems should be evaluated at each visit when a physical examination is performed, and any abnormalities recorded. A complete physical examination includes assessments of cardiovascular, respiratory, and neurological systems, as well as examination of the abdomen, lymph nodes, spleen, skin, oropharynx, and extremities.

5.6.2. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, at each visit during study drug, and at the Safety Follow-up Visit, as appropriate. Appendix 11 will be used to assess performance status.

5.6.3. Electrocardiogram

A 12-lead ECG will be performed in triplicate at screening, Cycle 1 Days 1, 3, 4, 22, 25 (Arm A only), and 28, and as clinically indicated (See Appendix 2, Appendix 3, and Appendix 4). Patients should be in the semi-recumbent or supine position.

5.6.4. Echocardiogram/Multigated Acquisition Scan

An echocardiogram or multigated acquisition scan will be performed locally at screening and when clinically indicated.

5.6.5. Adverse Events Review

Adverse events that occur during screening will be recorded on the medical history case report form and in the patient's source document.

After informed consent has been signed but prior to the administration of the study drug, only serious adverse events should be reported. After initiation of study drug, all adverse events and serious adverse events, 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 serious adverse events that are believed to be related to prior study drug treatment.

The adverse event reporting period is defined in Section 8.4.1.

All adverse events and serious adverse events will be followed until resolution, the condition stabilizes or is considered chronic, the adverse event or serious adverse event is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The accepted regulatory definition for an adverse event is provided in Section 8.1. Important additional requirements for reporting serious adverse events are explained in Section 8.6.

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

5.7. Efficacy Assessments

5.7.1. Efficacy Assessment for Mantle Cell Lymphoma, Marginal Zone Lymphoma, and Chronic Lymphocytic Lymphoma/Small Lymphocytic Lymphoma Patients

For patients with MCL, MZL, or SLL, response will be assessed and categorized per Lugano Classification for non-Hodgkin lymphoma NHL (Cheson et al, 2014; Appendix 9).

For patients with CLL, disease response will be determined in accordance with the 2018 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012) (Appendix 8).

5.7.2. Efficacy Assessment for Waldenström Macroglobulinemia Patients

Response in WM patients will be evaluated using an adaptation of the consensus panel criteria updated at the Sixth International Workshop (Owen et al 2013; NCCN Guidance Insights, 2012). Refer to Appendix 6 for response category definitions and guidelines for special clinical and laboratory circumstances.

5.7.3. Positron Emission Tomography and Computed Tomography

Computed tomography (CT) with contrast of chest, abdomen, and pelvis, and neck if clinically indicated, will be performed at screening and while on study until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Combined positron emission tomography/CT may be done at the discretion of the investigator and may be used in lieu of a CT with contrast only if the CT of the combined positron emission tomography /CT has been performed with diagnostic quality, adheres to the specified slice thickness/scan parameters, and intravenous contrast is administered. Otherwise, both scans should be done.

For patients with CLL/SLL, MCL, WM, MZL, and evidence of baseline extramedullary disease by CT scan, assessment by CT scan will occur every 12 weeks (end of Cycle 3 and 6).

Magnetic resonance imaging may be used in place of CT only for patients who cannot undergo CT due to contrast allergy but must be used consistently. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's course on study.

5.7.4. Bone Marrow Examination

Bone marrow biopsy (and aspirate for patients with CLL or WM) is required during the Screening Period to assess bone marrow involvement of lymphoma or leukemia. If a patient has had bone marrow examination performed within 90 days prior to Cycle 1 Day 1, a repeat screening bone marrow biopsy/aspirate is not required.

Patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CR with incomplete bone marrow recovery (CLL only) are required to have a bone marrow examination to confirm CR or CR with incomplete bone marrow recovery. This should be performed within 40 days from the CT/magnetic resonance imaging meeting the criteria of CR or CR with incomplete bone marrow recovery. All the other clinical data should be collected within ± 14 days from the CT/magnetic resonance imaging (ie, complete blood count with

differential and physical examination). Repeat bone marrow biopsy and/or aspirate are also required if imaging results demonstrate a Richter Transformation in patients with bone marrow involvement of lymphoma or leukemia at baseline.

For patients with CLL, bone marrow biopsy should be performed at time of suspected progression due to anemia or thrombocytopenia (refer to Appendix 8).

5.7.5. Endoscopy

Endoscopy may be performed at screening for patients with gastrointestinal involvement of their MCL and MZL. Patients who had an endoscopy performed during the screening period that confirmed gastrointestinal involvement of disease will require an endoscopy to confirm complete response. If a repeat biopsy cannot be obtained, a positron emission tomography scan that clearly documents continued disease clearance maybe used in lieu of the repeat biopsy.

5.8. Laboratory Assessments

Assessments will be performed at the timepoints specified in Appendix 2, Appendix 3, and Appendix 4 and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first study drug administration. Screening blood tests performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1.

Samples for hematology, clinical chemistry, coagulation profile (baseline), and quantitative immunoglobulin (for WM patients only) will be drawn and analyzed locally.

5.8.1. Hematology

Hematology parameters will be collected per standard of care at each site.

In the event of neutropenia (ANC $< 750/mm^3$) or thrombocytopenia (platelet count $< 50{,}000/mm^3$), these assessments will be conducted and collected as frequently as the investigator deems necessary until toxicity resolves to ≤ Grade 2 or returns to baseline (ANC $\geq 750/mm^3$).

Complete blood count with differential is required to be performed at screening, Days 1, 4, and 22 of Cycle 1, and at Day 1 of Cycles 2 to 6 during the Treatment Phase and at the Safety Follow-up Visit. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential, including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils.

5.8.2. Chemistry

Serum chemistry is required to be performed at screening, Days 1, 4, and 22 of Cycle 1, and at Day 1 of Cycles 2-6 during the Treatment Phase and at the Safety Follow-up Visit. Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase.

In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted and collected as frequently as the investigator deems necessary until toxicity resolves to ≤ Grade 2.

5.8.3. Quantitative Immunoglobulin

Quantitative immunoglobulin (Ig; IgG, IgM, IgA) will be measured on Day 1 of every cycle during the 6 cycles of Treatment Phase, with Cycle 1 Day 1 sample drawn at predose.

It is recommended that sequential response assessments for individual patients be performed in the same local laboratory using the same methodology.

For Waldenström Macroglobulinemia patients, changes in serum IgM level from baseline will be based upon the IgM value from the quantitative immunoglobulin assay, unless this is not possible due to assay limitations, in which case the M-protein level by densitometry will be used. Per International Workshop on WM criteria, progressive disease (PD) by increase in IgM requires a confirmatory blood draw which should be obtained at the next scheduled IgM draw or at a minimum of 4 weeks from the previous draw. In addition, PD requires a total increase of IgM of ≥ 500 mg/dL from nadir. Patients should remain on study drug until the laboratory IgM testing confirms PD. Transformation of WM to large cell lymphoma (Richter Transformation) is considered as PD and should not be recorded in the eCRF as an adverse event.

If there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" PD (eg, an increase in serum IgM level of ≥ 25% and ≥ 500 mg/dL from nadir) after the study drug has been held for at least 7 consecutive days, an assessment response of IgM flare will be assigned instead of PD. The period to which this is applicable begins on the day of the first missed dose and ends when the patient has IgM level or extramedullary disease that no longer qualify as "apparent" PD (eg, there is a decrease in serum IgM level to < 25% and < 500 mg/dL from nadir) or the patient has a confirmed PD, whichever occurs first. During and following periods of study drug withholding, response assessments that would otherwise qualify as PD will initially be recorded as IgM flare and NOT be considered as PD. See Appendix 6 for all conditions and timing that must be met when assigning response for IgM flare.

Patients may undergo plasmapheresis, when clinically indicated, during screening and the first 2 cycles of zanubrutinib. A pre-plasmapheresis serum total IgM and M-protein level should be obtained during the Screening Period that can serve as the baseline value for response assessment throughout the study.

Quantitative immunoglobulin (IgM, IgG, IgA), serum protein electrophoresis with quantification of M-protein by densitometry and serum immunofixation electrophoresis will be drawn as specified in the Schedule of Assessments (Appendix 2, Appendix 3, and Appendix 4).

5.8.4. Cold Agglutinins, Cryoglobulin, Anti-Myelin Associated Glycoprotein, and Serum Viscosity for Waldenström Macroglobulinemia Patients

Cold agglutinins, cryoglobulin, anti-MAG antibody, and serum viscosity blood tests may be performed at screening per site standard of care. If there are abnormal findings for any of these laboratory assessments at screening, follow-up is required per standard of care at their institution (at minimum at response timepoints per schedule of assessments) and at time of suspected CR.

5.8.5. 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.

5.8.6. HIV, Hepatitis B and Hepatitis C Testing

Viral hepatitis B (HBV) and C (HCV) serologic markers and/or viral load will be tested at screening.

The hepatitis B testing includes HBsAg, hepatitis B core antibody, and hepatitis B surface antibody, as well as HBV DNA by polymerase chain reaction (PCR) if the patient is negative for HBsAg but hepatitis B core antibody positive (regardless of hepatitis B surface antibody status). The HCV 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, hepatitis B core antibody positive, and HBV DNA negative must undergo monthly HBV DNA testing 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 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drug should be held and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped, and antiviral therapy should be initiated. Patients positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA testing. Patients with detected HCV RNA should stop study drug and antiviral therapy should be initiated. The medical monitor or designee should be informed of any suspected hepatitis B or hepatitis C reactivation.

Patients with known HIV are excluded from the study, as described in exclusion criteria (Section 4.2).

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 (or at least every 90 days for patients receiving prophylactic antiviral therapy)*	**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: HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.

5.8.7. Pregnancy Test

A serum pregnancy test will be performed at screening within 7 days of the first dose of study drug and at 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 Cycle 1 Day 1, and then on Day 28 of every cycle (which can be performed on Day 1 of the following cycle).

Pregnancy tests must be continued every 4 weeks (cycle) for at least 90 days after the last dose of study drug. At the last dose of study drug, a serum pregnancy test is required (for practicality, it will be performed at the End-of-Treatment Visit). 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 study drug administration will be immediately withdrawn from participation in the study.

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; Eastern Cooperative Oncology Group performance status; adverse event review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; 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. Treatment Phase and End-of-Treatment

The Treatment Phase (6 months) starts with the first day of assigned study drug and continues until the last dose of study drug has been taken/received.

All patients, regardless of reason for discontinuation of study drug, will undergo an End-of-Treatment Visit within 7 days of stopping study drug. A visit should be scheduled as soon as possible, at which time all of the assessments listed for the End-of-Treatment Visit will be performed (see Appendix 2, Appendix 3, and Appendix 4). The reason for discontinuation from treatment will be recorded on the eCRF.

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

- Disease progression
- Adverse event(s)
- Withdrawal of consent
- Investigator decision
- Other (including positive pregnancy test).

Patients who continue to derive clinical benefit from zanubrutinib in the presence of acceptable tolerability at the end of the Treatment Phase (6 cycles) may be eligible to continue to receive zanubrutinib under a rollover extension study.

Patients who discontinue treatment before 6 cycles will be followed post-treatment for survival in a rollover extension study.

5.11. Safety Follow-Up Visit

All patients who discontinue study drug prior to completion of 6 cycles and patients who discontinue study drug at the end of 6 cycles (ie, are not continuing treatment in a rollover extension study) that agree to a follow-up visit, will have a Safety Follow-up Visit approximately 30 days after the last dose of study drug. The Safety Follow-up Visit will collect adverse events and serious adverse events that may have occurred after the patient discontinued from the study drug. All treatment-related serious adverse events will be followed until resolution or stabilization. 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.

5.12. End of Study

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

- Withdrawal of consent. Patients may voluntarily withdraw consent from the study at any time.
- Death.
- Study termination by sponsor.
- Completion of 6 cycles of treatment.
- Other.

5.13. Lost to Follow-Up

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

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

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

6. STUDY DRUG

6.1. Study Drug Preparation and Dispensation

6.1.1. Packaging and Labeling

Zanubrutinib capsules will be provided in a child resistant high-density polyethylene bottle with induction seal and bottle label.

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 (59°F to 86°F).

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

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(s) dispensed and used by each patient. This information must be captured in the source document at each patient visit. Actual times of zanubrutinib and CYP3A inhibitor drug administration should be recorded during the study. Patients will be provided with patient diaries. The patient is responsible for maintaining the patient diary. The patient will record the number of zanubrutinib capsules and study drugs taken and if any were missed. The site personnel responsible for drug accountability will record the quantity of drug dispensed and quantity of drug received after the cycle visit. The patient diaries and the pharmacist's record of drug will be assessed by the investigator/study personnel at each 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

All doses will be administered in the morning with approximately 240 mL of room temperature water. When zanubrutinib is coadministered with a CYP3A inhibitor drug, a total of 240 mL of room temperature water will be given with both drugs. On days that zanubrutinib will be coadministered with a CYP3A inhibitor drug, zanubrutinib should be administered prior to the inhibitor.

On PK sampling days (Days 3 [alone], 10 [with fluconazole (Arm A) or voriconazole (Arm B)], and 28 [with diltiazem (Arm A) or clarithromycin (Arm B)]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. A predose-only PK sample will be taken on Day 22. On these PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). The morning doses of fluconazole, diltiazem, and clarithromycin are to be administered together with zanubrutinib.

6.2.1. Zanubrutinib

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the Treatment Phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Patients will be requested to bring their unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

Zanubrutinib will be administered at a 320 mg total daily dose using 80-mg capsules on days of administration as monotherapy (at a reduced dose of 80 mg twice a day [Arm A] and 80 mg once a day [Arm B] on Days 11 and 12 and Days 29 and 30 during washout).

When coadministered with CYP3A inhibitors, zanubrutinib will be administered at 80 mg twice a day (when used with a moderate CYP3A inhibitor) and 80 mg once a day (when used with a strong CYP3A inhibitor), with or without food.

On PK sampling days (Days 3, 10, 22 [predose only] and 28), zanubrutinib will be administered with food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Patients 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, then return to normal dosing with next dose. If a patient vomits after taking the capsules, that dose should not be repeated.

6.2.2. Fluconazole

Patients in Arm A will receive fluconazole 400 mg once a day, given orally as 2 x 200-mg tablets, from Day 4 to Day 10, along with zanubrutinib (at a reduced dose of 80 mg twice a day). Fluconazole tablets may be taken with or without food.

6.2.3. Diltiazem

Patients in Arm A will receive diltiazem 180 mg once a day, given orally as 1 x 180-mg extended release capsule, from Day 22 to Day 28, while patients receive zanubrutinib (at a reduced dose of 80 mg twice a day). Diltiazem capsules may be taken with or without food.

6.2.4. Voriconazole

Patients in Arm B will receive voriconazole 200 mg twice a day, given orally as 2 x 200-mg tablets, from Day 4 to Day 10, while patients receive zanubrutinib (at a reduced dose of 80 mg once a day). Voriconazole tablets should be taken at least 1 hour before or at least 1 hour after meals. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast.

6.2.5. Clarithromycin

Patients in Arm B will receive oral clarithromycin 250 mg twice a day, given as 2 x 250-mg immediate release tablets, from Day 22 to Day 28, while patients receive zanubrutinib (at a reduced dose of 80 mg once a day). Clarithromycin tablets may be taken with or without food.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered an overdose. Adverse events associated with an overdose or incorrect administration of study drug will be recorded on the adverse event eCRF. Any serious adverse events associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via serious adverse events reporting process as described in Section 8.6.1. There is no specific antidote for zanubrutinib. In an event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

6.4. Dose Interruption and Modification

The guidelines set forth in Table 2 should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.4.1) or nonhematologic (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 6.4.2) toxicities. During Cycle 1, when zanubrutinib is coadministered with CYP3A inhibitors, the investigator will consult with the medical monitor regarding dose reduction guidance.

Table 2: Zanubrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Zanubrutinib dose
First	0 = starting dose	320mg once a day or 160 mg twice a day
Second	-1 dose level	Restart at 80 mg twice a day
Third	-2 dose level	Restart at 80 mg once a day
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 sponsor's medical monitor.

6.4.1. Zanubrutinib Dose Reductions 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 the full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

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

6.4.2. Zanubrutinib Dose Reductions for Nonhematologic Toxicity

The guidelines set forth in Table 3 should be followed for dose interruption or modification of zanubrutinib for nonhematologic toxicities.

Table 3: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Restart Dose
≥ Grade 3 bleeding not considered related to study drug	Hold until recovery to less than or equal 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.	Restart at dose level -1.

Toxicity	Action for Zanubrutinib	Restart Dose
Any grade intracranial hemorrhage	Permanently discontinue zanubrutinib.	Not applicable.
Atrial fibrillation (AF) that is symptomatic and/or incompletely controlled	Hold until AF is controlled.	Restart 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.	Restart at the original dose level.

Abbreviations: AF, atrial fibrillation; BL, baseline; HTN, hypertension
During Cycle 1, when zanubrutinib is coadministered with CYP3A inhibitors, the investigator will consult with the medical monitor regarding dose reduction guidance.

Zanubrutinib should be withheld for any ≥ Grade 3 bleeding. The study drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of a rebleed is deemed acceptable. Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For nonhematological toxicities ≥ Grade 3, other than hypertension adequately controlled with oral medication or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1 or baseline and then restarted at original dose level.

If the event recurs at ≥ Grade 3, study drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -1. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 and restarted at level -2. If the event recurs at ≥ Grade 3 at level -2, the patient will be discontinued from study drug.

For patients experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled, study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.8.6.

7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

Medications taken within 4 weeks before study entry and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, will be recorded on the eCRF and in the patient's source documents.

All prior therapies for the B-cell malignancy will be recorded on the eCRF with the dates of administration.

Per the study eligibility criteria, patients who received certain prior medications and therapies (eg, exposure to a BTK inhibitor) are excluded from study participation.

7.2. Concomitant Therapy

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

All concomitant procedures performed during the study will be recorded in the eCRF.

Prophylactic measures against infection, for the prevention of bacterial or fungal infections, and/or for the prevention of hepatitis B infection reactivation should be used per institutional standards. However, to avoid interference with results of the DDI assessment, eligible patients will need to discontinue these medications 14 days prior to study drug dosing.

7.2.1. Permitted Medications

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines.
- Corticosteroids for indications other than the patient's B-cell malignancies.

  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-non-Hodgkin lymphoma-related conditions (eg, to treat a flare of chronic obstructive pulmonary disease).

  Chronic systemic corticosteroid use is not permitted, except for adrenal replacement, and requires consultation with the medical monitor.
- Therapy to reduce symptoms per standard of care and institutional guidelines.

Tumor lysis syndrome has been infrequently reported with zanubrutinib treatment, particularly in patients who were treated for CLL. Patients with high tumor burden should be monitored closely and treated as appropriate. Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are predisposed 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, prophylaxis should be considered as per institutional standards.

7.2.2. Prohibited Medications

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

Patients should not receive treatment with strong and moderate CYP3A inhibitors (other than those specified in the current study) or inducers or with drugs which are not allowed to be used in combination with diltiazem, clarithromycin, fluconazole or voriconazole.

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

7.3.1. Effects of Cytochrome P450-Inhibiting/Inducing Drugs on Exposure of Zanubrutinib

Administration of strong/moderate CYP3A inhibitors or CYP3A inducers should be prohibited during the first 30 days (Cycle 1), except those specifically prescribed per protocol.

Furthermore, administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 10 for a list of these medications), grapefruit juice, and Seville oranges should be done with caution, as they may affect the metabolism of zanubrutinib (Section 1.1.1.2). 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 guidance in Table 4. The medical monitor should be consulted in these situations. Please refer to Drug Interactions table for a more complete list.

Table 4: Dose Modification for Zanubrutinib when Coadministered with Strong/Moderate CYP3A Inhibitors or Inducers (Cycles 2 to 6)

CYP3A	Coadministered drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once a day
	Moderate CYP3A inhibitor (eg, diltiazem, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice a day (applicable beyond Cycle 1)
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort) and moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use

7.3.2. Effects of Zanubrutinib on Exposure of Other Concomitant Medications

A clinical DDI study (Study BGB-3111-108) indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.1.1.2). 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-t} and 34% for C_{max} (Section 1.1.1.2). The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution because zanubrutinib may increase their concentrations.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an adverse event or serious adverse events as provided in this protocol.

8.1. Adverse Events

8.1.1. Definitions and Reporting of an Adverse Event

An adverse event 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 adverse event include:

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

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

8.1.2. Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. Adverse events and serious adverse events should be assessed and graded based upon the NCI-CTCAE v5.0 (NCI, 2017).

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

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

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

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific adverse event, 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.

8.1.2.1. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each adverse event or serious adverse event using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the adverse event or serious adverse events to the study drug should be considered and investigated. The investigator should also consult the Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a serious adverse event 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 assessment of causality for every serious adverse event prior to transmission of the serious adverse event report to the sponsor, because 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 serious adverse event report/eCRF accordingly.

The causality of each adverse event should be assessed and classified by the investigator as "related" or "not related." An adverse event is considered related if there is "a reasonable possibility" that the adverse event 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 adverse event to the administration of study drug/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An adverse event 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 adverse event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the adverse event (eg, the patient's clinical condition or other concomitant adverse events).

8.1.2.2. Following Adverse Events

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

All adverse events and serious adverse events documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All adverse events and serious adverse events will be followed until resolution, the condition stabilizes or is considered chronic, the adverse event or serious adverse event is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the adverse event or serious adverse event. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, 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 adverse event or serious adverse event. 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 should be reported to the sponsor according to the serious adverse event instructions provided to the site within the time frames outlined in Section 8.6.1.

8.1.3. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as adverse events or serious adverse events. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are laboratory test abnormalities that are associated with clinical signs or symptoms, require active medical intervention, lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or further diagnostic investigation.

8.2. Definition of a Serious Adverse Event

A serious adverse event 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 adverse event in which the patient was at risk of death at the time of the adverse event; it does not refer to an adverse event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is considered a significant medical adverse event 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 serious adverse events:

- 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 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, the specificity or severity of which is not consistent with those noted in the 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 serious adverse events should be reported to sponsor. Any arising or worsening condition experienced by the patient after signing the informed consent but prior to first dose of study drug that does not meet the definition of serious should be reported only as medical history.

All adverse events which meet the definition of adverse event as specified in Section 8.1.1, and serious adverse events, 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 serious adverse events that are believed to be related to prior study drug treatment.

8.4.2. Eliciting Adverse Events

The investigator or designee will ask about adverse events 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, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an adverse event term. Similarly, nonserious adverse events which are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious adverse event is due to disease progression, it should be recorded as an adverse event. All serious adverse events and deaths, regardless of relatedness to disease progression, should be recorded and reported.

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. Reporting of Serious Adverse Events

8.6.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an adverse event meets the protocol definition of a serious adverse event, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All serious adverse events	Within 24 hours of first knowledge of the adverse event	Serious adverse event report	As expeditiously as possible	Serious adverse event report	Email or fax serious adverse event form

8.6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an serious adverse event has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined in Section 8.6.1. The serious adverse event report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding a serious adverse event, he/she is not to wait to receive additional information before notifying the sponsor or designee of the serious adverse event and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality at the time of the initial report as described in Section 8.1.2.1.

The sponsor will provide contact information for serious adverse event report submission.

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all serious adverse events to the sponsor in accordance with the procedures detailed in Section 8.6.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of serious adverse events to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 8.3) will be submitted to all applicable regulatory authorities and investigators for BGB-3111 studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person 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 drug or within 90 days after the last dose of zanubrutinib, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

8.8. Poststudy Adverse Event

A poststudy adverse event or serious adverse event is defined as any adverse event that meets the definition of adverse event as specified in Section 8.1.1 that occurs after the adverse event/serious adverse event reporting period, defined in Section 8.4.1.

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

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

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

To determine the reporting requirements for individual serious adverse events, the sponsor will assess the expectedness of the serious adverse events using the zanubrutinib Investigator's Brochure.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the sponsor or designee after the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Study Endpoints

9.1.1. Primary Endpoint

The primary endpoint assesses PK parameters including $AUC_{0\text{-}t}$, AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$), C_{max}, time to reach the C_{max} (T_{max}), and apparent terminal elimination half-life ($t_{1/2}$) as determined by blood samples collection during Cycle 1 on Day 3, Day 10, and Day 28.

9.1.2. Secondary Endpoints

The secondary endpoints include:

- Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs.

9.1.3. Exploratory Endpoints

The exploratory endpoints include:

- Overall response rate, defined as the proportion of patients who achieve a partial response or higher for MCL and MZL patients, and partial response with lymphocytosis for CLL/SLL patients. For WM patients, overall response rate is defined as the proportion of patients achieving CR, very good partial response, partial response, or minor response.
- Rate of CR or complete metabolic response, defined as the proportion of patients who achieve a CR or complete metabolic response.
- Time to response, defined as time from randomization to the first documentation of response.

9.2. Statistical Analysis

9.2.1. Analysis Sets

The PK evaluable analysis set will include all patients who received at least 1 dose of zanubrutinib and have evaluable PK data (at least 1 PK parameter can be calculated). A patient may be excluded from the PK summary statistics and statistical analysis if the patient has an AE of vomiting that occurs at or before 2 times the median T_{max} of zanubrutinib.

The Safety Analysis Set includes all patients who received at least 1 dose of zanubrutinib. The Safety Analysis Set will be used for all efficacy and safety analyses.

9.2.2. Subject Disposition

The number of patients enrolled and treated will be summarized. The primary reason for study drug discontinuation and end of study will be summarized.

9.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized.

9.2.4. Prior and Concomitant Therapy

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and therapeutic classifications. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as:

- Medications started before the first dose of study drug and were continuing at the time of the first dose of study drug, or
- Medications started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

Concomitant medications will be summarized by drug and therapeutic class. Listing of prior medications, concomitant medications, and concomitant procedures will be provided.

9.2.5. Pharmacokinetic Analyses

The following PK parameters will be assessed for zanubrutinib: C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0–24h}$, and $t_{1/2}$ on Day 3 in the absence of CYP3A inhibitors and on Day 10 and Day 28 in the presence of CYP3A inhibitors. Additional PK parameters may be calculated as needed.

PK analyses will be performed by standard noncompartmental analysis methods using Phoenix® WinNonlin™ version 7.0 or higher (Certara USA, Inc., Princeton, New Jersey).

The geometric mean ratios of PK parameters of zanubrutinib with and without coadministration of the inhibitors and the associated 90% confidence intervals will be constructed based on the least squares means and intrapatient coefficient of variation from a mixed effects model of log transformed PK parameters.

9.2.6. Efficacy Analysis

Summaries of efficacy will be provided separately for each histologic subtype and for the pooled subtypes. Overall response rate, rate of CR or complete metabolic response, and time to response based on the investigator's assessment using standard response criteria for each histologic subtype are exploratory efficacy endpoints and will be analyzed for the Safety Analysis Set.

- The estimated overall response rate and a 2-sided 95% exact binomial confidence interval for overall response rate will be provided.
- Rate of complete response or complete metabolic response will be analyzed using the same methods employed for overall response rate.
- Time to response will be summarized by sample statistics such as mean, median, and standard deviation for responders only.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all adverse events graded by NCI-CTCAE v5.0. Laboratory values (hematology or clinical chemistry), vital signs, physical examinations, and ECG findings will also be used in assessing safety.

All summaries of the safety data will be provided for each arm and for the pooled arms based on the Safety Analysis Set.

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose reductions, dose interruptions, and permanent discontinuation of study drug due to adverse events will be summarized. Frequency of reductions and dose interruptions will be summarized by categories.

9.3.2. Adverse Events

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities terms and graded according to the NCI-CTCAE v5.0 (NCI, 2017).

All treatment-emergent adverse events will be summarized. A treatment-emergent adverse event is defined as an adverse event that had an onset date on or after the first dose of study drug up to 30 days after the last treatment with zanubrutinib or was worsening in severity from baseline (pretreatment) but before the date of starting any new anticancer therapy, whichever occurs first.

Treatment-emergent adverse events of any grade, serious adverse events, treatment-emergent adverse events ≥ Grade 3, treatment-emergent adverse events leading to treatment discontinuation, dose reduction, dose interruption, death, and treatment-related adverse events will be summarized. Treatment-emergent adverse events will also be summarized by system organ class, preferred term, and worst grade. A patient will be counted only once by the highest severity grade within a system organ class and preferred term, even if the patient experienced more than 1 treatment-emergent adverse event within a specific system organ class and preferred term. Treatment-related adverse events include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. Incidence and time to selected treatment-emergent adverse events of special interest will also be summarized.

The number of deaths and the cause of death will also be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology and clinical chemistry) values will be evaluated for each laboratory parameter. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Laboratory values and change from baseline will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded per NCI-CTCAE v5.0 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately. Change from baseline to the worst postbaseline grade will be summarized.

9.3.4. Vital Signs

Vital sign parameters (systolic and diastolic blood pressure, heart rate, body temperature, and weight) and changes from baseline will be summarized by visit.

9.3.5. Electrocardiogram

A summary of ECG parameters at screening will be provided.

9.4. Sample Size Consideration

Approximately 30 patients will be enrolled in the study to ensure that 12 patients per arm successfully complete Cycle 1.

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations. Approximately 30 patients with B-cell malignancies (15 in each arm) will be enrolled to ensure that 24 patients (12 in each arm) complete the study.

10. STUDY COMMUNICATION

10.1. 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.

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 will be undetermined at such an early stage of research.

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

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

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Conference on Harmonisation guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations 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 in accordance with Good Clinical Practices and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

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

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 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 consent form for documenting written informed

consent. Each informed consent will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

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

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.6.3, the investigator (or sponsor, where applicable) is responsible for reporting serious adverse events to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the 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 consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only date of independent central review and an identification code (ie, not patient 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 study.

The investigator agrees that all information received from sponsor, 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 sponsor 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 sponsor. 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 a written contract for the conduct of the study is executed that includes confidentiality provisions 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 promptly entered into an electronic data capture system; data should be entered into the electronic data capture system within 5 business days from the time of collection, unless otherwise indicated in the site contract.

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 Form Food and Drug Administration 1572, must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

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

The 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.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the Medical Dictionary for Regulatory Activities.

11.2.8. 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 sponsor and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with sponsor requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these

procedures. If the site cannot meet sponsor's requirements for disposal, arrangements will be made between the site and sponsor 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.

11.2.9. Inspections

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

11.2.10. 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 and shall immediately report all protocol deviations to sponsor.

11.2.11. 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 to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with sponsor 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's last visit).

11.3. Protocol Modifications

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

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

11.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Sponsor 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 sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2013).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review 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. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of 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.

11.5. Study and Study Center Closure

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

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

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

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If

required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

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

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

11.6. Records Retention and Study Files

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

The investigator's study file will contain the protocol/amendments, 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 regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

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

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

11.7. Information Disclosure and Inventions

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

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

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

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

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 11.4.

If a written contract for the conduct of the study which includes provisions inconsistent with this Section 11.7 is executed, that contract's provisions shall apply rather than this Section 11.7.

11.8. Joint Investigator/Sponsor Responsibilities

11.8.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice 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 in the course of these monitoring visits are resolved.

11.8.2. Access to Information for Auditing or Inspections

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

12. REFERENCES

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APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A drug–drug interaction study of zanubrutinib with moderate/strong CYP3A inhibitors in patients with B-cell malignancies

PROTOCOL NO: BGB-3111-113

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

Instructions for 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: _____

Name/Address of Center: _____

_____

_____

APPENDIX 2. SCHEDULE OF ASSESSMENTS

	Pretreatment	Treatment Phase		End-of-Treatment Visit	Safety Follow-up Visit
	Screening	**Cycle 1 (30 days)**	**Cycles 2-6 (28 days)**		
Day of cycle	**-28 to -1**			**≤ 7 days after last dose**	**30 days after last dose**
Window (Days)	–		**± 7**		
Informed consent[a]	X	Appendix 3 and Appendix 4			
Inclusion/exclusion criteria[b]	X				
Demography[c]	X				
Medical/surgical history/current medical conditions[d]	X				
Randomization	X				
B-cell malignancy diagnosis[e]	X				
12-lead ECG[f]	X				
ECHO/MUGA[g]	X				
ECOG performance status	X		X	X	X
Height (cm)	X				
Weight (kg)/ vital signs / physical examination / symptoms assessment/ review for arrhythmia signs/symptoms[h]	X		X	X	X
Hematology[i]	X		X		X
Chemistry[i]	X		X		X

	Pretreatment	Treatment Phase		End-of-Treatment Visit	Safety Follow-up Visit
	Screening	**Cycle 1 (30 days)**	**Cycles 2-6 (28 days)**		
Day of cycle	**-28 to -1**			**≤ 7 days after last dose**	**30 days after last dose**
Window (Days)	–		**± 7**		
β2-microglobulin[i]	X				
Coagulation[i]	X				
Quantitative immunoglobulin (QIG)[i]	X		X	X	
WM only: SPEP with M-protein quantitation by densitometry and serum IFE[i]	X		X	X	
WM only: Cold agglutinins, cryoglobulin, anti-MAG antibody, serum viscosity[i]	X		For any abnormal result at screening, follow-up is required per standard of care (at minimum at response timepoints per schedule of assessments), and at time of suspected CR.		
Hepatitis B/C testing[i]	X		Viral hepatitis B and C serologic markers and/or viral load will be tested at screening. Patient negative for HBsAg, HBcAb positive, and HBV DNA negative must undergo monthly HBV DNA testing by PCR.		
CT scan[j]	X		Every 12 weeks (end of Cycle 3 and Cycle 6)		
Whole body FDG-PET scan or integrated PET/CT scan	X		At the time of CR (if PET positive as screening)		
Bone marrow examination[k]	X		At time of complete response if positive at screening or suspected Richter Transformation		
Endoscopy[l]	X		At time of CR if confirmed gastrointestinal involvement at screening		

	Pretreatment	Treatment Phase		End-of-Treatment Visit	Safety Follow-up Visit
	Screening	**Cycle 1 (30 days)**	**Cycles 2-6 (28 days)**		
Day of cycle	**-28 to -1**			**≤ 7 days after last dose**	**30 days after last dose**
Window (Days)	–		**± 7**		
Pregnancy test (if applicable)[i]	X (within 7 days of first dose of study drug)		X	Every 28 days (cycle) for at least 90 days after the last dose of study drug	
Prior and concomitant medications[m]	Throughout study		X		
Prior and concomitant procedures[m]	Throughout study		X		
Adverse events/Serious adverse events	Throughout study		X	X	X
Study drug administration/dispensation (zanubrutinib) (Arm A and B)[n]			X		
Fluconazole (Arm A)[n]					
Diltiazem (Arm A)[n]					
Voriconazole (Arm B)[n]					
Clarithromycin (Arm B)[n]					
PK collection (when applicable)			Appendix 5		

Abbreviations: CLL, chronic lymphocytic leukemia; C_{max}, time to maximum plasma concentration; CR, complete response; CT, computed tomography; ECG, electrocardiogram; eCRF, electronic case report form; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; FDG-PET, fluorodeoxyglucose positron emission tomography; 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; IFE, immunofixation electrophoresis; Ig, immunoglobulin; MAG, myelin associated glycoprotein; MCL, mantle cell lymphoma; MUGA, multigated acquisition; MZL, marginal zone lymphoma; PCR, polymerase chain reaction; PET, positron emission tomography; PK, pharmacokinetic; QIG, quantitative immunoglobulin; SPEP, serum protein electrophoresis; WM, Waldenström macroglobulinemia.

Time between randomization and Day 1 should be no more than 5 days. Assessments scheduled on Cycle 1 Day 1 should be performed before the administration of the first dose of zanubrutinib. Screening blood performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

a. 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.

b. Screening evaluations will be performed and completed within 28 days of the first dose of study drug. The results of all screening assessments and evaluations must be completed and reviewed by the investigator before Cycle 1 Day 1. The investigator will review and ensure that the patient meets all of the inclusion and none of the exclusion. 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 randomizing the patient in the Interactive Response Technology system.

c. Demography includes gender, year of birth (and/or age), and race/ethnicity.

d. Relevant medical history (ie, previous diagnoses, diseases, or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the patient's study eligibility, and current medical conditions.

e. Diagnosis and extent of cancer, includes background information such as history of disease and current disease status, staging (at time of diagnosis and at time of treatment), bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant nondrug therapies will be collected.

f. Perform a 12-lead ECG in triplicate at screening, during Cycle 1 as indicated, and anytime when clinically indicated. Patients should be in the semi-recumbent or supine position.

g. Perform ECHO or MUGA at the local laboratory at screening and/or when clinically indicated.

h. Physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature), weight, and B-symptoms examination will be performed at the timepoints specified. A complete physical examination includes assessments of cardiovascular, respiratory, and neurological systems as well as the examination of the abdomen, lymph nodes, spleen, skin, oropharynx, and extremities. Clinical suspicion of progressive disease at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B-symptoms include unexplained weight loss > 10% over previous 6 months, fever (≥ 38°C), and/or drenching night sweats. Data collected at each visit will be recorded in the eCRF.

i. Laboratory assessments include the following:

1 Screening clinical laboratory assessments performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1. Screening QIG (IgG, IgM, IgA) (all patients), SPEP with M-protein quantitation by densitometry and IFE (WM patients), performed within 14 days of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

2 **Hematology parameters** will be collected as protocol defined timepoints and as per standard of care. Complete blood count with differential is required to be performed at screening and at every visit during the Treatment Phase and at the Safety Follow-up Visit. Complete blood count includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils.

3 **Clinical chemistry** parameters will be collected per standard of care at each site. Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, LDH, and alkaline phosphatase.

4 **Coagulation** profile will be performed at screening only and includes activated partial thromboplastin time and prothrombin time, which will also be reported as international normalized ratio.

5 **Quantitative immunoglobulins** (IgG, IgM, IgA) will be measured on Day 1 of every cycle during the 6 cycles of Treatment Phase, with Cycle 1 Day 1 sample drawn at predose.

6 **Serum protein electrophoresis with M-protein quantitation** by densitometry and IFE will be performed at screening, predose on Cycle 1 Day 1, and on Day 1 of every cycle for patients whose response will be based on M-protein (and not IgM). The screening SPEP with M-protein quantitation by densitometry and IFE, performed within 14 days of the first administration of study drug, do not need to be repeated on Cycle 1 Day 1.

7 **Cold agglutinins, cryoglobulin; anti-MAG and serum viscosity** are not mandatory tests and should be performed at screening and thereafter for WM patients as per site's standard of care. If there are abnormal findings for any of these laboratory assessments at screening, follow-up is suggested as per standard of care at their institution during the 6 cycles of Treatment Phase, and at time of suspected complete response.

8 **Hepatitis B/C** serologic markers and viral load will be tested at screening only. 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 negative for HBsAg, HBcAb positive, and HBV DNA negative must undergo monthly HBV DNA testing by PCR. Patients positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA testing. Patients with known HIV are excluded from the study.

9 All women of childbearing potential (including those who have had a tubal ligation) will have a **serum pregnancy test** at screening within 7 days of first dose of study drug. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Cycle 1 Day 1, then on Day 28 of every cycle (which can be performed on Day 1 of the following cycle). Any female patient who is pregnant will not be eligible for the study. Urine or serum pregnancy tests must be continued every 28 days (cycle) for at least 90 days after the last dose of study drug. At the last dose of study drug, a serum pregnancy test is required. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

j. For patients with WM, postbaseline imaging is only required for those with evidence of baseline extramedullary disease. A CT scan does not need to be repeated at end of treatment if performed within 45 days before the Safety Follow-up Visit.

k. Bone marrow biopsy (all patients) and/or aspirate (for patients with WM and CLL) is required during screening to assess bone marrow involvement of lymphoma or leukemia. If a patient has had bone marrow examination performed within 90 days prior to Cycle 1 Day 1, a repeat bone marrow biopsy/aspirate is not required. Repeat bone marrow biopsy (for all patients) and/or aspirate (for patients with WM and CLL) are required if imaging results demonstrate a complete response in patients with bone marrow involvement of lymphoma or leukemia at baseline. Repeat bone marrow biopsy and/or aspirate are also required if imaging results demonstrate a Richter Transformation in patients with bone marrow involvement of lymphoma or leukemia at baseline. For patients with CLL, bone marrow biopsy should be performed at time of suspected progression due to anemia or thrombocytopenia.

l. For patients with MCL or MZL, endoscopy may be performed at screening for patients with gastrointestinal involvement of their disease. Patients who had an endoscopy performed during the Screening Period which confirmed gastrointestinal involvement of their disease will require an endoscopy to confirm CR. If a repeat biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance maybe used in lieu of the repeat biopsy.

m. Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 28 days before Cycle 1 Day 1, and on study thereafter.

n. Zanubrutinib at 320 mg orally once a day will be used during drug-drug interaction assessment in Cycle 1 to allow for wider exposure coverage for C_{max} (320 mg once a day dose has approximately 2 times higher C_{max} than that of 160 mg twice a day dose) in the presence of CYP3A inhibitor treatment. After PK assessment in Cycle 1, patients will receive 320 mg once a day or 160 mg twice a day from Cycle 2 to Cycle 6. Zanubrutinib will be dosed at 80 mg twice a day and 80 mg once a day when coadministered with a moderate or strong CYP3A inhibitor in Arm A and Arm B, respectively. For Arm A: from Day 4 to Day 10, fluconazole will be administered once a day at a dose of 400 mg; and from Day 22 to Day 28, diltiazem will be administered once a day at a dose of 180 mg. For Arm B: from Day 4 to Day 10, voriconazole will be administered twice a day at a dose of 200 mg; and from Day 22 to Day 28, clarithromycin will be administered twice a day at a dose of 250 mg. All patients will continue with zanubrutinib treatment (160 mg twice a day or 320 mg once a day) until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or end of study (completion of 6 cycles), whichever

occurs first. Patients enrolled in the rollover extension study will receive 160 mg twice a day or 320 mg once a day doses. On PK sampling days (Days 3 [alone], 10 [with fluconazole (Arm A) or voriconazole (Arm B)], and 28 [with diltiazem (Arm A) or clarithromycin (Arm B)]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). On days where PK samples are not collected, zanubrutinib can be taken with or without food. The morning doses of fluconazole, diltiazem, and clarithromycin are to be administered together with zanubrutinib. All patients will have an End- of-Treatment visit within 7 days after stopping study drug. All patients will have a Follow-Up Visit 30 days after the last dose of the study drug to collect adverse events and serious adverse events that may have occurred after the patient discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.

APPENDIX 3. CYCLE 1 ARM A SCHEDULE OF ASSESSMENTS

	Cycle 1 - Arm A																														
Day of Week	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**
Day of Cycle 1	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Window (Days)	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**
Clinic Visit	X		X	X						X												X			X			X		
ECOG performance status	X		X	X						X												X			X			X		
Weight (kg)/ vital signs/ physical examination / symptoms assessment/ review for arrhythmia signs/symptoms[b]	X		X	X						X												X[g]			X			X		
Prior and concomitant medications[c]	X		X	X						X												X			X			X		
Prior and concomitant procedures[c]	X		X	X						X												X			X			X		
Adverse events/serious adverse events	X		X	X						X												X			X			X		
ECG	X		X[h]	X						X												X[h]			X			X		
Hematology and chemistry[d]	X			X																		X						X		
QIG (IgG, IgM, IgA)[d]	X																													
WM patients only: SPEP and IFE[d]	X																													
Pregnancy test[e]	X																													
Zanubrutinib[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluconazole (Arm A)[f]				X	X	X	X	X	X	X																				
Diltiazem (Arm A)[f]																						X	X	X	X	X	X	X		
PK collection (Appendix 5)			X							X												X						X		

Abbreviations: C_{max}, time to maximum plasma concentration; ECG, electrocardiogram; eCRF, electronic case report form; ECOG, Eastern Cooperative Oncology Group; IFE, immunofixation electrophoresis; Ig, immunoglobulin; PK, pharmacokinetic; QIG, quantitative immunoglobulin; SPEP, serum protein electrophoresis; WM, Waldenström macroglobulinemia.

a. Cycle 1 Day 1 testing and zanubrutinib dispensation may be completed within 72 hrs before the prescribed Cycle 1 Day 1 first zanubrutinib dose date. To avoid visits occurring over weekends, Cycle 1 Day 1 should be scheduled for a Tuesday.

b. Physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature), weight, and B-symptoms examination will be performed at the timepoints specified. A complete physical examination includes assessments of cardiovascular, respiratory, and neurological systems as well as the examination of the abdomen, lymph nodes, spleen, skin, oropharynx, and extremities. Clinical suspicion of progressive disease at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B-symptoms include unexplained weight loss > 10% over previous 6 months, fever (≥ 38°C), and/or drenching night sweats. Data collected at each visit will be recorded in the eCRF.

c. Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 28 days before Cycle 1 Day 1, and on study thereafter.

d. Screening clinical laboratory assessments (hematology and chemistry) performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1. Screening QIG (IgG, IgM, IgA) (all patients), SPEP with M-protein quantitation by densitometry and IFE (WM patients), performed within 14 days of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

e. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening within 7 days of first dose of study drug.

f. Zanubrutinib at 320 mg orally once a day will be used during drug-drug interaction assessment in Cycle 1 to allow for wider exposure coverage for C_{max} (320 mg once a day dose has approximately 2 times higher C_{max} than that of 160 mg twice a day dose) in the presence of CYP3A inhibitor treatment. After PK assessment in Cycle 1, patients will receive 320 mg once a day from Cycle 2 to Cycle 6. Zanubrutinib will be dosed at 80 mg twice a day when coadministered with a moderate CYP3A inhibitor. From Day 4 to Day 10, fluconazole will be administered once a day at a dose of 400 mg; and from Day 22 to Day 28, diltiazem will be administered once a day at a dose of 180 mg. All patients will continue with zanubrutinib treatment (160 mg twice a day or 320 mg once a day) until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or end of study (completion of 6 cycles), whichever occurs first. Patients enrolled in the rollover extension study will receive 160 mg twice a day or 320 mg once a day doses. On PK sampling days (Days 3 [alone], 10 [with fluconazole], and 28 [with diltiazem]), zanubrutinib is to be administered 30 minutes after a low-fat breakfast. On days where PK samples are not collected or on Day 22 (predose only), zanubrutinib can be taken with or without food. The morning doses of fluconazole and diltiazem are to be administered together with zanubrutinib. All patients will have an End- of-Treatment visit within 7 days after stopping study drug. All patients will have a Follow-up Visit 30 days after the last dose of the study drug to collect adverse events and serious adverse events that may have occurred after the patient discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.

g. At Day 22 blood pressure measured predose, 1, 2, 3, and 4 hrs postdose.

h. ECG predose and 2 hrs postdose (zanubrutinib) on Days 3, 10, and 28; predose and 4 hrs postdose at Day 22; and predose only at other timepoints. Postdose ECGs should be completed within ± 15 minutes of timepoints.

APPENDIX 4. CYCLE 1 ARM B SCHEDULE OF ASSESSMENTS

	Cycle 1 - Arm B																														
Day of Week	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**
Day of cycle 1	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Window (Days)	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**	**±0**
Clinic Visit	X		X	X						X												X						X		
ECOG performance status	X		X	X						X												X						X		
Weight (kg)/ vital signs / physical examination / symptoms assessment/ review for arrhythmia signs/symptoms[b]	X		X	X						X												X						X		
Prior and concomitant medications[c]	X		X	X						X												X						X		
Prior and concomitant procedures[c]	X		X	X						X												X						X		
Adverse events/Serious adverse events	X		X	X						X												X						X		
ECG	X		X[g]	X						X[g]												X						X[g]		
Hematology and chemistry[d]	X			X																		X						X		
QIG (IgG, IgM, IgA)[d]	X																													
WM patients only: SPEP and IFE[e]	X																													
Pregnancy test[e]	X																													
Zanubrutinib[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Voriconazole (Arm B)[f]				X	X	X	X	X	X	X																				
Clarithromycin (Arm B)[f]																						X	X	X	X	X	X	X		
PK collection (Appendix 5)			X							X												X						X		

Abbreviations: C_{max}, time to maximum plasma concentration; ECG, electrocardiogram; eCRF, electronic case report form; ECOG, Eastern Cooperative Oncology Group; IFE, immunofixation electrophoresis; Ig, immunoglobulin; PK, pharmacokinetic; QIG, quantitative immunoglobulin; SPEP, serum protein electrophoresis; WM, Waldenström macroglobulinemia.

a. Cycle 1 Day 1 testing and zanubrutinib dispensation may be completed within 72 hrs before the prescribed Cycle 1 Day 1 first zanubrutinib dose date. To avoid visits occurring over weekends, Cycle 1 Day 1 should be scheduled for a Tuesday.
b. Physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature), weight, and B-symptoms examination will be performed at the timepoints specified. A complete physical examination includes assessments of cardiovascular, respiratory, and neurological systems as well as the examination of the abdomen, lymph nodes, spleen, skin, oropharynx, and extremities. Clinical suspicion of progressive disease at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B-symptoms include unexplained weight loss > 10% over previous 6 months, fever (≥ 38°C), and/or drenching night sweats. Data collected at each visit will be recorded in the eCRF.
c. Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 28 days before Cycle 1 Day 1, and on study thereafter.
d. Screening clinical laboratory assessments (hematology and chemistry) performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1. Screening QIG (IgG, IgM, IgA) (all patients), SPEP with M-protein quantitation by densitometry and IFE (WM patients), performed within 14 days of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.
e. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening within 7 days of first dose of study drug.
f. Zanubrutinib at 320 mg orally once a day will be used during drug-drug interaction assessment in Cycle 1 to allow for wider exposure coverage for C_{max} (320 mg once a day dose has approximately 2 times higher C_{max} than that of 160 mg twice a day dose) in the presence of CYP3A inhibitor treatment. After PK assessment in Cycle 1, patients will receive 320 mg once a day or 160 mg twice a day from Cycle 2 to Cycle 6. Zanubrutinib will be dosed 80 mg once a day when coadministered with a strong CYP3A inhibitor. From Day 4 to Day 10, voriconazole will be administered twice a day at a dose of 200 mg; and from Day 22 to Day 28, clarithromycin will be administered twice a day at a dose of 250 mg. All patients will continue with zanubrutinib treatment (160 mg twice a day or 320 mg once a day) until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or end of study (completion of 6 cycles), whichever occurs first. Patients enrolled in the rollover extension study will receive 160 mg twice a day or 320 mg once a day doses. On PK sampling days (Days 3 [alone], 10 [with voriconazole], and 28 [clarithromycin], zanubrutinib is to be administered 30 minutes after a low-fat breakfast. On PK sampling days, the morning dose of voriconazole is to be administered 1 hour before a low-fat breakfast (zanubrutinib administered 30 minutes after the low-fat breakfast). On days where PK samples are not collected or on Day 22 (predose only), zanubrutinib can be taken with or without food. The morning doses of fluconazole, diltiazem and clarithromycin are to be administered together with zanubrutinib. All patients will have an End- of-Treatment visit within 7 days after stopping study drug. All patients will have a Follow-Up Visit 30 days after the last dose of the study drug to collect adverse events and serious adverse events that may have occurred after the patient discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
g. ECG predose and 2 hrs postdose (zanubrutinib) on Days 3, 10, and 28 and predose only at other timepoints. Postdose ECGs should be completed within ± 15 minutes of timepoint.

APPENDIX 5. PHARMACOKINETIC BLOOD SAMPLING (ZANUBRUTINIB)

Arm A and Arm B

Cycle 1									
Hours	**Predose[a]**	**0.5[b]**	**1[b]**	**2[c]**	**3[c]**	**4[c]**	**6[c]**	**8[c]**	**10[c]**
Day 3	X	X	X	X	X	X	X	X	X
Day 10	X	X	X	X	X	X	X	X	X
Day 22	X								
Day 28	X	X	X	X	X	X	X	X	X

Abbreviations: C, cycle; D, day; PK, pharmacokinetics.

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

a. Within 2 hours prior to dosing.

b. The window period is ± 5 minutes.

c. The window period is ± 10 minutes.

APPENDIX 6. WALDENSTRÖM MACROGLOBULINEMIA RESPONSE CATEGORY DEFINITIONS

Response category	Definition
Complete response (CR)	Normal serum IgM values Disappearance of monoclonal protein by immunofixation No histological evidence of bone marrow involvement Complete resolution of lymphadenopathy/splenomegaly (if present at baseline)
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline or normal serum IgM values Improvement in extramedullary disease, lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	≥ 50% reduction of serum IgM from baseline Reduction in lymphadenopathy/splenomegaly (if present at baseline)
Minor response (MR)	At least 25% but < 50% reduction of serum IgM from baseline
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	At least one of the following: • Confirmed ≥ 25% increase in serum IgM and total increase of ≥ 500 mg/dL from nadir (on treatment)[a,b] • New lymph nodes > 1.5 cm, or ≥ 50% increase from nadir in sum product of diameter (SPD) of > 1 node, or ≥ 50% increase in longest diameter of a previously identified node • New splenomegaly or ≥ 50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

Source: modified from Owen et al 2013

a. Sequential changes (separated by at least 4 weeks) in IgM levels should be determined by the IgM value from the quantitative immunoglobulin assay, unless for assay limitations this is not possible, in which case the M-protein level by densitometry (SPEP) will be used.

b. If there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" response of PD (eg, there is an increase in IgM level of ≥ 25% and ≥ 500 mg/dL from nadir) after the study drug has been held for at least 7 consecutive days, an assessment of IgM flare will be assigned instead of PD. The period to which this is applicable begins on the day of the first missed dose and ends when the patient has IgM level or extramedullary disease that no longer qualify as "apparent" PD or the patient has a confirmed response of PD, whichever comes first. Please see guidelines for specific clinical or laboratory circumstances and timing below.

Guidelines for specific clinical or laboratory circumstances:

1. **Baseline serum total immunoglobulin M (IgM) value above the laboratory limit of quantitation**

   If the baseline laboratory serum total IgM value exceeds the upper limit of quantitation, the M-protein value, by central assessment, will be used for response determination throughout the study.

2. **Baseline serum total IgM value, by central assessment, is not interpretable due to technical reasons**

   If the baseline laboratory serum total IgM value is not interpretable due to technical reasons, the laboratory serum M-protein value will be used for response determination throughout the study. In cases where both the laboratory total serum IgM and M-protein values are not interpretable due to technical reasons, the local serum total IgM (or local M-protein value, in cases where the local serum total IgM value exceeds the upper level of quantitation) will be used for response assessment throughout the study.

3. **Patients with documented cryoglobulinemia**

   For patients with abnormal cryoglobulin result at screening, the local laboratory will retest for the presence of cryoglobulins before Cycle 1 Day 1. The Cycle 1 Day 1 sample will serve as the baseline. In addition, quantitative immunoglobulin should be retested using the residual cryoglobulin blood sample at the local laboratory, which should be collected and processed under warm conditions. Only when serum immunoglobulin levels cannot be quantified, serum protein electrophoresis sample will need to be re-collected, processed, and analyzed at the local laboratory under warm conditions. The blood samples (for cryoglobulin and serum immunoglobulins) should be collected and processed under warm conditions at the local laboratory throughout the study to ensure that the same methodology is used throughout the study. The samples should NOT be sent to the central laboratory.

4. **Plasmapheresis**

   Patients may undergo plasmapheresis, when clinically indicated. A pre-plasmapheresis serum total IgM and M-protein level should be obtained during the Screening Period that can serve as the baseline value for response assessment throughout the study.

   Patients who receive plasmapheresis may be evaluated for the effects of plasmapheresis on zanubrutinib concentrations. Patients will receive zanubrutinib in the clinic prior to the plasmapheresis procedure (plasmapheresis is to commence between 0.5 to 2 hours following zanubrutinib dosing). For those who consent, plasma samples will be collected immediately before the start of plasmapheresis, approximately 1 hour after the start of the procedure, and 30 min after the end of procedure. Zanubrutinib dosing time and the start and end time of each plasmapheresis session must be recorded in the database. Plasma zanubrutinib concentrations will be measured using a validated method.

5. **Assigning IgM Flare due to study drug hold**

   An assessment of IgM flare will be assigned instead of progressive disease (PD) after study drug has been held at least 7 consecutive days and there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" response of PD. The period that this is applicable begins on the day of the first missed dose and ends when the patient has IgM levels or extramedullary disease that no longer qualify as "apparent" PD (eg, there is a drop in IgM level below 25% and 500 mg/dL from nadir) or the patient has a confirmed response of PD, whichever comes first.

6. **When assigning response for IgM flare after drug is restarted, the following conditions must be met:**

a. If IgM levels and/or known extramedullary disease continue to decrease from peak IgM level (off study drug) or peak (highest sum of the product of the perpendicular diameter [SPD]) in extramedullary disease, when drug was held, PD will not be recorded. If, however, while on study drug the IgM level or SPD increases above the peak level that occurred when drug was held, and IgM level or SPD increase is confirmed with a repeat assessment 4 weeks later, the patient will be considered to have PD and IgM will not be assessed.
b. If, after 10 weeks of study drug reinitiation (to allow for fluctuation), the next assessed IgM level shows either a continued rise at each timepoint from the initiation of the drug hold or no decrease from the previous visit, then a serum IgM level obtained 4 weeks later must be used to confirm PD. Progressive disease will be confirmed if the subsequent IgM measurement is greater than or equal to the previous IgM assessment (first IgM assessment after 10 weeks study drug initiation). The response assessment of PD will be recorded at the first visit 10 weeks after study drug reinitiation.
c. Similarly, if apparent PD was due to an increase in extramedullary disease and after 10 weeks of study drug reinitiation the evaluation of extramedullary shows either a continued rise from the initiation of the drug hold or no decrease from the previous visit, then PD is confirmed and the response assessment of PD will be recorded at the first visit 10 weeks after study drug reinitiation.
d. If during drug reinitiation the IgM level decreases and then rises at any timepoint thereafter:

   – If at the time of the IgM rise, the IgM level still qualifies as PD, then a confirmatory serum IgM level obtained 4 weeks later must be used to confirm PD. Progressive disease will be confirmed if the subsequent IgM measurement is greater than or equal to the previous IgM assessment (IgM at the time of the initial IgM rise following IgM decrease). The response of PD will be recorded at the time of the initial IgM following the IgM decrease.

   – If at the time of the IgM rise, the IgM level does not qualify as PD, then continue response assessments as described above.

Of note, in the setting of multiple drug holds, the nadir continues to be the lowest achieved serum IgM level on study for purposes of response assessment.

Progressive disease is defined per protocol as an increase in serum IgM level of at least 25 % and at least 500 mg/dL from nadir.

APPENDIX 7. INDICATION FOR INITIATION OF THERAPY IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

Clinical indications for initiation of therapy

- Recurrent fever, night sweats, weight loss, fatigue
- Hyper viscosity
- Lymphadenopathy which is either symptomatic or bulky (≥ 5 cm in maximum diameter)
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to Waldenström macroglobulinemia (WM)

Laboratory indications for initiation of therapy

- Symptomatic cryoglobulinemia
- Cold agglutin anemia
- Immune hemolytic anemia and/or thrombocytopenia
- Nephropathy related to WM
- Amyloidosis related to WM
- Hemoglobin ≤ 10 g/dL
- Platelet count < 100 x 10^9/L

Adapted from Dimopoulos et al 2014.

APPENDIX 8. RESPONSE DEFINITION AFTER TREATMENT FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Parameter	CR[a]	PR	PR-L	PD	SD
Group A					
Lymph Nodes	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)[b]	Decrease ≥ 50% from baseline	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
Liver and/or spleen size[c]	Spleen size < 13cm; liver size normal	Decrease ≥ 50% (from baseline)	Decrease ≥ 50% from baseline	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
Constitutional symptoms	None	Any	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	Increase ≥ 50% from baseline[d]	Change of -49% to +49%
Group B					
Platelet count	≥ 100 x 10^9/L	≥ 100 x 10^9/L or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 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	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
Bone marrow biopsy	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

Source: Hallek et al 2018; Cheson et al 2012

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete remission (response); CRi, CR with incomplete bone marrow recovery; PD, disease progression; PR, partial remission (response); PR-L, partial remission (response) with lymphocytosis; SD, stable disease

Parameters of Group A assess the lymphoid tumor load and constitutional symptoms; parameters of Group B asses the hematopoietic system. CR: all of the criteria have to be met; PR: at least 2 of the parameters of Group A and 1 parameter of Group B need to improve if previously abnormal; if only 1 parameter of both Groups A and B is abnormal before therapy, only 1 of either Group A or Group B needs to improve; PR-L: presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for platelets, hemoglobin, or bone marrow biopsy have to be met; PD: at least 1 of the criteria of Group A or Group B has to be met; SD: all of the criteria have to be met, constitutional symptoms alone do not define PD.

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 (defined as vertical spleen length > 13 cm) during periods of zanubrutinib hold will not be considered as disease progression 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.

a. Some patients fulfill all the criteria for a CR, but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CRi. For the definition of this category, the marrow evaluation should be performed with scrutiny and not show any clonal disease infiltrate.

b. Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and by physical examination).

c. Spleen size is considered normal if < 13 cm.

d. In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD (Cheson et at, 2012).

APPENDIX 9. LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

Response and site	PET-CT-based response (Patients with PET-avid disease at screening)	CT-based response (Patients without PET-avid disease at screening)
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extralymphatic sites	Score 1, 2, 3* with or without a residual mass on 5-point scale▪ It is recognized that in Waldeyer's ring or extranodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• 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	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, immunohistochemistry negative
Partial	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5▪ with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	• ≥ 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	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

(Continued on the next page)

Response and site	PET-CT-based response (Patients with PET-avid disease at screening)	CT-based response (Patients without PET-avid disease at screening)
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5▪ with no significant change in FDG uptake from baseline at interim or end of treatment	< 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	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease Score 4 or 5▪ with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	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
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

(Continued on next page)

Response and site	PET-CT-based response (Patients with PET-avid disease at screening)	CT-based response (Patients without PET-avid disease at screening)
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• 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 FDG-avid foci	New or recurrent involvement

Source: modified from Cheson et al 2014.

Abbreviations: CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

▪PET 5-point scale (Deauville Criteria):
- 1: no uptake above background
- 2. uptake ≤ mediastinum
- 3. uptake > mediastinum but ≤ liver
- 4. uptake moderately > liver
- 5. uptake markedly higher than liver and/or new lesions

X. new areas of uptake unlikely to be related to lymphoma

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 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 10. CYP3A INHIBITORS AND INDUCERS

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

Strong CYP3A inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone, idelalisib
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
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), Seville oranges
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
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 Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Also refer to the Flockhart Table: http://medicine.iupui.edu/clinpharm/ddis/main-table and the Australian Medicines Handbook (AMH) for a list of CYP inhibitors, inducers and substrates

APPENDIX 11. Eastern Cooperative Oncology Group 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 housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

As published by Oken et al, 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 12. 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.

Abbreviation: NYHA, New York Heart Association.