CLINICAL RESEARCH PROTOCOL

Protocol Title:	**A Phase I, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies**
Protocol Number:	**BGB-3111-AU-003**
Phase:	**1**
Investigational Product:	**Zanubrutinib (BGB-3111)**
Sponsor:	**BeiGene, Ltd.** **c/o BeiGene Aus Pty Ltd,** **1C/528 Compton Road Stretton** **Queensland 4116, Australia** **BeiGene, Ltd.** **c/o BeiGene USA, Inc.** **2929 Campus Drive, Suite 300** **San Mateo, CA 94403, USA**
Sponsor Medical Monitor:	[redacted] **Telephone:** **Email:** [redacted]
Coordinating Investigator:	[redacted]
Date of Protocol Version:	**25 September 2018** **Version 8**

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FINAL PROTOCOL APPROVAL SHEET

PROTOCOL TITLE: A Phase I, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies

PROTOCOL NO: BGB-3111-AU-003

BeiGene, Ltd. Approval:

[redacted]

27 Sep 2018

Date

SYNOPSIS

Name of Sponsor/Company:	**BeiGene, Ltd.**
Name of Finished Product:	**Zanubrutinib (BGB-3111)**
Name of Active Ingredient:	**Zanubrutinib (BGB-3111)**
Title of Study:	A Phase I, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies
Protocol No:	BGB-3111-AU-003
Study centers:	Multiple study centers in Australia, New Zealand, USA, Europe, and South Korea.
Study duration: Screening; daily treatment until disease progression, intolerance or death, withdrawal of consent, loss to follow-up, or study termination by sponsor; safety follow-up until 28 days after last dose of study drug	Phase: 1

Objectives:

Part 1 (Dose Escalation)

Primary:

- To determine the safety and tolerability of zanubrutinib (also known as BGB-3111) in patients with B-cell malignancies.
- To determine the recommended Phase 2 dose (RP2D) and regimen of zanubrutinib when given continuously orally.

Secondary:

- To characterize the pharmacokinetics (PK) of zanubrutinib after drug administration.
- To determine the extent of Bruton tyrosine kinase (BTK) inhibition in peripheral blood mononuclear cells (PBMCs) after treatment with zanubrutinib.
- To describe the preliminary antitumor activity of zanubrutinib.

Exploratory:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Part 2 (Expansion)

Expansion to determine additional safety and efficacy at the RP2D for the various Cohorts

Primary:

- To further assess the safety and tolerability of zanubrutinib, administered orally either once a day (QD) or twice a day (BID), in patients with specific B-cell malignancies.

Secondary:

- To assess the preliminary antitumor activity of zanubrutinib at RP2D(s) in patients with specific

B-cell malignancies.

- To further characterize the PK profile of zanubrutinib.
- To determine the extent of BTK inhibition in peripheral blood mononuclear cells (PBMCs) after treatment with zanubrutinib.

Exploratory:

- [redacted]

Methodology:

This is a multicenter, Phase 1, open-label, multiple-dose, dose escalation, first-in-human (FIH) study. It is to be conducted in two sequential parts: Dose Escalation (Part 1), followed by Expansion (Part 2).

Part 1 (Dose Escalation)

The study will follow a modified 3+3 dose escalation scheme.

At least 3 patients will be enrolled into each cohort. Additional patient(s), up to a maximum of 6 patients in total, will be enrolled if more than 3 have been screened and are eligible for the cohort. The dose limiting toxicity (DLT) assessment and dose escalation scheme will follow the same principle as stipulated for a standard 3+3 dose escalation design. For example, 3 additional patients will be enrolled if a DLT is observed in 1 of 3 patients; 2 additional patients will be enrolled if a DLT is observed in 1 of 4 patients; and 1 additional patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1of 6 patients. No additional patients will be treated at a given dose level if 2 or more of the patients in the cohort develop a DLT during DLT assessment period. In this instance, the maximum tolerated dose (MTD) is considered to have been exceeded.

The starting dose will be 40 mg/day (once daily). The period for DLT assessment is 21 days from first dose of zanubrutinib. Evaluation of a cohort of at least 3 patients completing DLT assessment at any given dose level is required prior to determining the next dose level and dose regimen for the subsequent cohort. Pharmacodynamic effect of zanubrutinib on BTK inhibition will be studied in PBMCs and in lymph nodes if available.

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. A Safety Monitoring Committee (SMC) will be established for the determination of dose levels to be administered and dose regimen during dose escalation and will utilize the data available from the previous dose levels.

In the event that a MTD is not identified due to paucity of DLTs, the Expansion schedule will be based on PK, pharmacodynamic studies of BTK inhibition in PBMCs, safety, tolerability, and preliminary efficacy.

Patients who were enrolled under the QD dosing schedule will have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib (revised per Version 6).

Part 2 (Expansion)

All cohorts in the Expansion portion of the study will enroll in parallel with the exception of 2g (mantle cell lymphoma [MCL] patients), which will be initiated after the enrollment of Cohort 2a is complete. Patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) will be assigned to either Cohort 2c or Cohort 2e by alternate allocation until Cohort 2c is filled. Patients with R/R Waldenström's macroglobulinemia (WM) will be assigned to either Cohort 2d or Cohort 2f by

alternate allocation until Cohort 2d is filled. Patients with treatment naïve (TN) WM will be assigned to Cohort 2f. Cohort 2h and Cohort 2i will not be open to the sites in South Korea.

- Cohort 2a will evaluate the RP2D, given on 2 dosing schedules (QD vs BID) in approximately 40 patients with R/R MCL, follicular lymphoma (FL), marginal zone lymphoma (MZL), or germinal center B-cell like (GCB) subtype of diffuse large B-cell lymphoma DLBCL. Patients will be assigned to either the QD dosing schedule that receives the RP2D, or the BID dosing schedule that receives 50% of the RP2D, by alternate allocation based on tumor types. Zanubrutinib safety and efficacy will be assessed. Patients who were enrolled under the QD dosing schedule will have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib (revised per Version 6). Patients in both cohorts will undergo a lymph node biopsy (unless none accessible or judged to be unsafe) at screening stage and before their day 3 dose – ie, either 10-14 or 22-26 hours post dose, depending on assigned schedule - for pharmacodynamic studies of BTK inhibition in lymph nodes, in addition to that in PBMCs.
- Cohort 2b will evaluate the safety and efficacy of zanubrutinib at the RP2D given at the BID dosing schedule (50% of the RP2D) in approximately 40 patients with R/R non-GCB subtype of DLBCL, defined by Hans algorithm.
- Cohort 2c will evaluate the safety and efficacy of zanubrutinib given on the BID dosing schedule (50% of the RP2D) in approximately 70 patients with R/R CLL/SLL.
- Cohort 2d will evaluate the safety and efficacy of zanubrutinib given on the BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R WM.
- Cohort 2e will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R CLL/SLL (revised per Version 6). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2f will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 50 patients with TN or R/R WM (revised per Version 6), requiring treatment per the International Workshop on WM guidelines. Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. For United Kingdom (UK) Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2g will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R MCL (revised per Version 6). This cohort will be initiated after the enrollment in Cohort 2a is complete. Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2h will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with TN CLL/SLL (Revised per Version 6), requiring treatment per IWCLL guidelines. Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2i will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with TN MCL, with age ≥ 65 and comorbidity score ≥ 6 using the cumulative illness rating scale (CIRS) (revised per Version 6).

Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.

- Cohort 2j will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 10 patients with R/R hairy cell leukemia (HCL) (revised per Version 6). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2k will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 40 patients with R/R indolent lymphoma, defined as FL, MZL, or mucosa-associated lymphoid tissue (MALT) lymphoma.
- Cohort 2l will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 15 patients with Richter's transformation. Patients with prior BTK inhibitor treatment other than zanubrutinib will be allowed to enroll in this cohort.
- Cohort 2m will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 15 patients with R/R B-cell malignancy (otherwise eligible for Cohorts 2a to 2l) who failed to achieve a major response (partial response [PR] or better) after at least 6 months, had disease progression on prior BTK-inhibitor therapy (ibrutinib, acalabrutinib, zanubrutinib, or other BTK-inhibitor therapy), or discontinued BTK-inhibitor therapy due to an AE. A minimal 7-day washout period is required before initiation of zanubrutinib treatment. All prior BTK inhibitor related AEs must have resolved to Grade 1 or less.

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. When at least 6 or more patients have been treated with zanubrutinib in an expansion cohort and ≥ 33% of the treated patients experience an event that would meet the definition of a DLT if the event happened during dose escalation study accrual will be held pending data review by the SMC.

This study will be considered complete once all patients have either manifested disease progression, ceased zanubrutinib due to intolerance, death, or withdrawal from the study.

Planned number of patients:	***Part 1:*** Approximately 25 patients during the Dose Escalation period. ***Part 2:*** Approximately 380 patients for Expansion.
Study population:	Inclusion criteria: 1. Aged ≥ 18 years, voluntarily consented to the study. 2. *Part 1 (Dose Escalation):* Relapsed or refractory World Health Organization (WHO) classification defined B-lymphoid malignancy following at least one line of therapy, with no therapy of higher priority available, with the exception of Burkitt lymphoma/leukemia, plasma cell myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, and plasmablastic lymphoma. 3. *Part 2 (Expansion):* • Cohort 2a: R/R WHO-defined MCL, FL, MZL, or GCB subtype of DLBCL defined by Hans algorithm. All patients must have at least one site of biopsiable lymph node. • Cohort 2b: R/R WHO-defined DLBCL, non-GCB

	subtype, defined by Hans algorithm. Patients must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype [redacted]. • Cohort 2c: R/R WHO-defined CLL/SLL. • Cohort 2d: R/R WHO-defined WM. • Cohort 2e: R/R WHO-defined CLL/SLL on QD or BID dosing. • Cohort 2f: WHO-defined WM requiring treatment, or TN WM, per the International Workshop on WM guidelines. For UK Patients: TN patients must be unsuitable for standard chemotherapy. • Cohort 2g: R/R WHO-defined MCL. • Cohort 2h: Previously untreated CLL/SLL requiring treatment per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines. This cohort is not open in South Korea. For UK Patients: TN patients must be unsuitable for standard chemotherapy. • Cohort 2i: Previously untreated MCL with age ≥ 65 and comorbidity score CIRS ≥ 6. This cohort is not open in South Korea. For UK Patients: TN patients must be unsuitable for standard chemotherapy. • Cohort 2j: R/R WHO-defined HCL. • Cohort 2k: R/R WHO-defined indolent lymphoma, (inclusive of FL, MZL, and MALT lymphoma). • Cohort 2l: Confirmed Richter's transformation of CLL/SLL. Patients who previously received a BTK inhibitor other than zanubrutinib are allowed. Patients to be enrolled must have histologic confirmation of Richter's transformation prior to enrollment. • Cohort 2m: Patient's with R/R B-cell malignancy (otherwise eligible for Cohorts 2a-2l) who failed to achieve a major response (PR or better) after at least 6 months, had disease progression on prior BTK-inhibitor therapy (ibrutinib, acalabrutinib, zanubrutinib, or other BTK-inhibitor therapy), or discontinued BTK-inhibitor therapy due to an AE. A minimal 7-day washout period is required before initiation of zanubrutinib treatment. All prior BTK inhibitor related AEs must have resolved to Grade 1 or less. 4. Requirement for treatment in the opinion of the investigator. 5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2. 6. Adequate hematologic function, as defined by neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L; patients with neutrophils < 1.0 x 10^9/L due to marrow infiltration are allowed to receive growth

	factors to bring pre-treatment neutrophils to ≥ 1.0 x 10^9/L; patients with platelets < 50 x 10^9/L due to marrow infiltration are allowed to receive platelet transfusion to bring pre-treatment platelets to ≥ 50 x 10^9/L. 7. Adequate renal function, as defined by creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation/ CKD-EPI equation or as measured by nuclear medicine scan or 24 hour urine collection). 8. Adequate liver function, as defined by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN), and bilirubin ≤ 1.5 x ULN (unless documented Gilbert's syndrome). 9. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN. 10. Female patients of childbearing potential and non-sterile males must practice at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, intrauterine device (IUD) or hormonal contraceptive initiated at least 3 months prior to first dose of study drug. • Female patients of childbearing potential and non-sterile males must practice highly effective methods of birth control initiated at least 3 months prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug. These methods include the following: o Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation ▪ Oral, intravaginal or transdermal o Progestogen-only hormonal contraception associated with the inhibition of ovulation ▪ Oral, injectable, implantable o An IUD o Intrauterine hormone-releasing system (IUS) o Bilateral tubal occlusion o Vasectomized partner o Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. • 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. 11. Male patients must not donate sperm from initial study drug

	administration, until 90 days after drug discontinuation. Key exclusion criteria: 1. Current central nervous system involvement by lymphoma or leukemia. 2. Current histologically transformed disease except patients in Cohort 2l. 3. Prior BTK inhibitor treatment except patients in Cohort 2l and Cohort 2m. 4. Allogeneic stem cell transplantation within 6 months or has active graft-versus-host disease (GVHD) requiring ongoing immunosuppression. 5. Receipt of the following treatment prior to first dose of zanubrutinib: corticosteroids given with antineoplastic intent within 7 days, chemotherapy or radiotherapy within 2 weeks, monoclonal antibody within 4 weeks. 6. Not recovered from toxicity of any prior chemotherapy to Grade ≤ 1. 7. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated *in situ* carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent. 8. Uncontrolled systemic infection requiring parenteral antimicrobial therapy. 9. Major surgery in the past 4 weeks. 10. Known infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows: • Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable. • Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable. 12. Cardiovascular disease resulting in New York Heart Association function status of ≥ 3. 13. QTcF > 480 msecs based on the Fridericia's formula or other significant electrocardiogram (ECG) abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min). 14. Significant active renal, neurologic, psychiatric, hepatic or endocrinologic disease that in the investigator's opinion would adversely impact on his/her participating in the study. 15. Inability to comply with study procedures. 16. On medications which are strong cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers. 17. Pregnant and breast-feeding women are excluded from the study.
Study drug, dose and mode	Zanubrutinib oral 20 mg and 80 mg capsules

of administration:	
Reference therapy, dose, and mode of administration:	Not applicable

Criteria for Evaluation:

Part 1 (Dose Escalation)

Primary Endpoints:

- The safety of zanubrutinib will be assessed throughout the study by monitoring adverse events (AEs), serious adverse events (SAEs), per the NCI-CTCAE Version 4.03, physical examination, and laboratory measurements.
- The RP2D and regimen of zanubrutinib will be determined based on PK, BTK inhibition in PBMCs, safety and tolerability and preliminary efficacy.

Secondary Endpoints:

- For a single dose profile: area under the plasma concentration time curve from zero to the last measurable concentration (AUC_{last}), area under the plasma concentration-time curve from zero to infinity (AUC), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).
- After steady-state ($_{ss}$): $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.
- Overall response rate (ORR), complete response rate (CRR), partial response rate (PRR), minimal residual disease (MRD) clearance rate, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).
- BTK inhibition activity of zanubrutinib in PBMCs will be determined via BTK occupancy assay.

Exploratory Endpoints:

- [redacted]

Part 2 (Expansion)

Primary Endpoint:

- The safety and tolerability of zanubrutinib will be further evaluated as described for Part 1.

Secondary Endpoints:

- ORR, CRR, PRR, MRD clearance rate, PFS, OS, and DOR.
- The PK profiles of zanubrutinib will be further characterized as described for Part 1.
- BTK inhibition activity of zanubrutinib in PBMCs will be determined via BTK occupancy assay.

Exploratory Endpoints:

- [redacted]

[redacted]

Statistical Methods:

Part 1 (Dose Escalation)

The number of dose levels examined and the emerging zanubrutinib toxicities will determine the sample size. It is anticipated that approximately 25 patients will be required to establish the RP2D(s) of zanubrutinib when administered as a single agent.

Data will be listed and summarized according to the sponsor agreed reporting standards, where applicable.

Part 2(Expansion)

Approximately 380 patients will be evaluated to examine the potential efficacy as well as safety and tolerability of zanubrutinib in patients with specific B-cell malignancies.

Data will be listed and summarized according to the sponsor-agreed reporting standards, where applicable.

All patients who are exposed to (or started receiving) the agent of zanubrutinib will be included in the safety analysis set. All patients for whom valid zanubrutinib PK parameters can be estimated will be included in the PK analysis set on an as treated basis. For other parameters, all evaluable data will be included in the summaries.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B-cell
AE	adverse event
AUC	area under the plasma concentration-time curve
BID	bis in die (twice a day)
BTK	Bruton tyrosine kinase
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CRO	clinical research organization
CRR	complete response rate
CT	computed tomography
DBP	diastolic blood pressure
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetra acetic acid
FDA	Food and Drug Administration
FDG	Flourodeoxyglucose
FIH	first-in-human
GCB	germinal center B-cell-like
GCP	Good Clinical Practices
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCL	hairy cell leukemia
HCV	hepatitis C virus
IB	Investigator's Brochure
IC_{50}	50% maximal inhibiting concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukemia

LN	lymph node
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetics
PO	orally
PR	partial response
PRR	partial response rate
QD	quaque die (once a day)
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SBP	systolic blood pressure
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOPs	Standard Operating Procedures
$t_{1/2}$	terminal half-life
t_{max}	time to maximum observed plasma concentration
TN	treatment naïve
Vd_{ss}	steady state volume of distribution
WBC	white blood cell
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

1. INTRODUCTION

1.1. Background and Pharmacology

Bruton tyrosine kinase (BTK), a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, is a critical component of the B-cell receptor (BCR) signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib has demonstrated promising antitumor activities in several B-cell malignancies, including mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), Waldenström's macroglobulinaemia (WM), and activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL). Ibrutinib is approved by the FDA for treatment of MCL and CLL in patients who had received at least one prior therapy. More recently it was also approved for the treatment of patients with CLL with 17p deletion (July 2014) and WM (January 2015) (ibrutinib prescribing information).

Zanubrutinib (also known as BGB-3111) is a potent, specific and irreversible BTK inhibitor. The data generated in preclinical studies using biochemical, cell based and animal studies suggest that zanubrutinib could offer significant patient benefit in inhibiting tumor growth in B-cell malignancies. Zanubrutinib was more selective than ibrutinib for inhibition of BTK compared with epidermal growth factor (EGFR), FGR, fyn-related Src family tyrosine kinase (FRK), human epidermal growth factor 2 (HER2), HER4, interleukin 2 (IL-2)-inducible T-cell kinase (ITK), Janus kinase 3(JAK3), lymphocyte-specific protein tyrosine kinase (LCK), and TEC, therefore may have fewer side-effects than ibrutinib in clinic. Consistent with its weaker ITK activity, zanubrutinib displayed significantly less inhibitory effect on inhibiting rituximab-induced antibody-dependent cellular cytotoxicity (ADCC) than ibrutinib. Zanubrutinib inhibited B-cell receptor (BCR) aggregation-triggered BTK autophosphorylation, blocked downstream phospholipase C gamma ($PLC\gamma_2$) signaling, and reduced cell proliferation in MCL and DLBCL cell lines tested.

In vivo studies demonstrate that zanubrutinib had dose-dependent antitumor activity against Rec-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib was significantly more effective than ibrutinib in both models. In pharmacokinetics/pharmacodynamics studies, oral administration of zanubrutinib resulted in time-dependent occupancy of BTK in blood and in spleen in mice.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of zanubrutinib (BGB-3111 Investigator's Brochure).

1.1.1. Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion

Zanubrutinib's oral bioavailability was moderate to good in rats, ranging from 9.3% to 41%, and good in dogs, ranging from 45% to 50%. Elimination half-lives ranged from 1.2 to 2.6 hours in rats and 1.4 to 3.9 hours in dogs after oral administration. Clearance was high in rats (52.3 mL/min/kg) and moderate in dogs (23.6 mL/min/kg). Steady state volume of distribution (Vd_{ss}) in rats and dogs was 1.4 L/kg and 1.7 L/kg, respectively.

The kinetics was linear over the dose range of 10 to 100 mg/kg in female rats, and 2.5 to 25 mg/kg in dogs. The linearity in male rats from 10 to 100 mg/kg was not as good, with the dose-normalized area

under the curve (AUC) at 30 mg/kg slightly higher, 2.1-fold ($p<0.05$) and 1.5-fold ($p>0.05$), than those at 10 mg/kg and 100 mg/kg, respectively. There was no accumulation of zanubrutinib following multiple oral dosing in both species. No significant gender difference in exposures was found in dogs. Exposures in female rats were higher compared with that in male rats (1.7 to 4.9-fold). This sex difference in rats, however, is not expected to be of clinical relevance as it reflects differences in elimination pathways in rats for which gender differences are much more pronounced than that in humans.

Plasma protein binding (PPB) for zanubrutinib was 94.2%, 93.9%, 93.3%, 96.7% and 94.9% in human, monkey, dog, rat, and mouse plasma, respectively. The blood-to-plasma ratios were 0.804 and 0.752 in humans and dogs, respectively, suggesting that zanubrutinib has a partitioning preference in plasma in humans and dogs. In rats, the blood-to-plasma concentration ratios of zanubrutinib was 0.766, 1.03, and 1.39 at 0.3, 3, and 30 μM, respectively, suggesting its red blood cells/plasma partition preference in rats is drug concentration-dependent.

After oral administration in rats at 30 mg/kg, zanubrutinib was detected in all organs checked. The maximum mean concentrations were detected at 0.25 hour post-dose in plasma, heart, liver, spleen, lung, kidney, stomach, and small intestine, and at 2 hours post-dose in all other organs with drug concentration in a descending order as following: stomach, small intestine, liver, kidney, heart, ovary, plasma, fat, spleen, muscle, lung, submandibular lymph node, skin, thymus gland, testicle, and brain. At 8 hours post-dose, the mean tissue concentrations of zanubrutinib decreased to 0-11% of the maximum concentrations in organ tissues except for testicle where the drug concentration was 56% of the maximum concentration. However, the drug concentration in testicle was very low even at the peak levels.

Zanubrutinib was considered to be a moderate to high turnover compound in human, monkey, dog, rat, and mouse liver microsomes, with lowest clearance rate in dog liver microsomes. A total of 11 metabolites of zanubrutinib (M1, M2, M3, M4, M5, M6, M7, M8, M9, M10 and M11) were identified in human, monkey, dog, rat, and mouse liver microsomes, while 11 metabolites (M3, M5, M6, M12, M13, M14, M15, M16, M17, M18 and M19) observed in plasma, urine, bile, and feces of rats after oral administration of zanubrutinib. These nineteen metabolites were proposed to be produced via hydroxylation, oxidative deamination, N-dealkylation, dehydration, dehydrogenation, glucuronidation, cysteine conjugation, acetylation and sulfation reactions.

Cytochrome P450 (CYP) phenotyping study using human liver microsomes with selective CYP inhibitors and recombinant CYP enzymes suggests that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism.

Zanubrutinib was a moderate inhibitor of CYP2C8 (IC_{50} = 4.03 μM), CYP2C9 (IC_{50} = 5.69 μM) and CYP2C19 (IC_{50} = 7.80 μM) while its IC_{50}s for other CYP isozymes were all > 10 μM. Drug-drug interactions between zanubrutinib and CYP2C8, CYP2C9, and CYP2C19 substrates would be dependent on final plasma levels obtained in humans at therapeutic doses. Zanubrutinib was not an inducer of human CYP1A2, CYP2B6 but had CYP3A induction potential at concentration ≥ 3 μM in primary human hepatocytes. Whether it induces CYP3A in human would also depend on final plasma levels obtained in humans at therapeutic doses.

The total recovery of cumulative excretion amounts of zanubrutinib in bile, urine, and feces in rats was low. Less than 0.1% was excreted in urine (up to 48 hours) and bile (up to 36 hours). After single and

multiple oral doses of zanubrutinib at 30 mg/kg, the cumulative excretion amounts in feces were 1.84% and 1.86% (up to 48 hours), respectively.

Refer to the IB for more detailed information on the pharmacokinetics (PK) and absorption, distribution, metabolism, and excretion (ADME) of zanubrutinib (BGB-3111 Investigator's Brochure).

1.2. Toxicology

The nonclinical toxicity profile of zanubrutinib was characterized in both rats and dogs in single and repeat dose studies up to 28 days. The zanubrutinib related changes included increase in white blood cells (WBC), neutrophils (NEUT) and fibroblasts (FIB); decrease in reticulocytes (RET), red blood cells (RBC), hemoglobin (HGB), and hematocrit (HCT); and shortened activated partial thromboplastin time (APTT). The systemic exposure increased dose proportionally without accumulation over 28-day duration in both rats and dogs; the sex difference in systemic exposure was only noted in rats with 1.8 to 2.9-fold higher exposure in female rats than in male rats. The histopathological changes in pancreas and skin of rats was considered to be adverse and other zanubrutinib-related histopathological changes were considered to be the physiological response or attributable to stress or no apparent adverse effects, including spleen, prostate gland, uterus, and large intestine; the changes in pancreas were mainly noted in male rats at and above 50 mg/kg/day without dose relevancy, but were recoverable following 28-day recovery time; the changes in skin were noted in the lip and/or nose in both sexes mainly at 500 mg/kg/day and not seen after 28-day recovery time. A moderate inhibition on human ether-a-go-go-related gene (hERG) current (half maximal inhibitory concentration [IC_{50}]) was noted at 5.71 μM, but no effects on blood pressure, heart rate, or electrocardiogram (ECG) were noted in telemetry-instrumented conscious dogs when dosing up to 100 mg/kg. No mutagenicity was noted in a mini Ames assay.

No mortality or severe toxicity was noted up to 1,000 mg/kg at single doses in both rats and dogs. No mortality or severe irreversible toxicity was noted in 28-day repeat dose studies at high doses of 500 or 100 mg/kg/day in rats or dogs, respectively. The systemic exposure at the high dose levels tested in both rats and dogs appeared to have achieved the projected approximately 50-fold of anticipated human exposure at the therapeutic dose. In summary, the available toxicological data support the clinical development of zanubrutinib in Phase 1 clinical trials for cancer patients.

Refer to the IB for current information on the toxicology of zanubrutinib (BGB-3111 Investigator's Brochure).

1.2.1. Studies in Rats

In a single dose acute toxicity study at 0, 250, 500 or 1,000 mg/kg followed by a 14-day observation, no mortality, abnormal clinical signs, or apparent changes in body weights, food consumption, and ophthalmology examination were noted in animals with the exception that slight short APTT was noted at 1,000 mg/kg. No zanubrutinib related organ weights or macroscopic changes were noted. Under the condition of this study, the maximal tolerated dose (MTD) was considered to be higher than 1000 mg/kg.

In a 14-day oral repeat dose study at 25, 75 or 250 mg/kg/day, no mortality, abnormal clinical signs, or apparent changes in body weights and food consumption were noted in animals with the exception of slight increase in WBC in females and slight increase in alanine aminotransferase (ALT) in both males and females at 250 mg/kg/day. The systemic exposure increased dose proportionally with 2.4 to 3.0-fold

higher exposure in females than in males on Day 10 following 10-day repeat dose. The MTD was considered to be higher than 250 mg/kg/day in this study.

In a 28-day oral repeat dose Good Laboratory Practice (GLP) study in rats at 0, 50, 150 or 500 mg/kg/day, no mortality occurred at any dose levels throughout the study. Zanubrutinib related clinical signs including scabs around nose, mouth, lip, and/or eyelid, soiled coat, salivation, abnormal stool, and lip/periorbital swelling were noted in males and/or females mainly at high dose of 500 mg/kg/day. A decrease (7%) in body weight gain was only noted in males at 500 mg/kg/day and slight increase in food consumption was noted in both males and females at ≥ 50 mg/kg/day. Increase in WBC, NEUT, RET, and red cell distribution width (RDW) and decrease in RBC, HGB and HCT were noted in males at 500 mg/kg/day and in females at ≥ 150 mg/kg/day on Day 28. No toxicologically significant changes in clinical chemistry or coagulation were noted throughout the study. Zanubrutinib related changes in urine were noted, including occult blood and/or RBC at ≥ 150 mg/kg/day and bilirubin at 500 mg/kg/day in males; and occult blood only at 500 mg/kg/day in females. All of these changes were not noted after the recovery phase. The systemic exposure ($AUC_{0\text{-}24h}$) increased dose proportionally in both sexes with 1.8 to 2.9-fold higher exposure in females than in males and no accumulation over 28-day duration. The slight organ weight changes were noted in liver and spleen in both males and females; in prostate and epididymis in males; and in ovary, uterus, adrenal, and thymus in females. The histopathological changes in pancreas and skin was considered to be adverse and other zanubrutinib-related histopathological changes were considered to be the physiological response or attributable to stress or no apparent adverse effects, including spleen, prostate gland, uterus, and large intestine; the changes in pancreas were mainly noted in male rats at and above 50 mg/kg/day without dose relevancy, but were recoverable following 28-day recovery time; the changes in skin were noted in the lip and/or nose in both sexes mainly at 500 mg/kg/day and not seen after 28-day recovery time. Based on the result of this study, the MTD was considered to be 500 mg/kg/day.

In summary, the toxicity profile of zanubrutinib was characterized in single and repeat dose studies in rats up to 28-day duration. No zanubrutinib related mortality, severe, or irreversible toxicity was noted at high dose of 500 mg/kg/day. The changes in clinical pathology were noted mainly at 500 mg/kg/day. The systemic exposure increased dose proportionally with 1.8 to 2.9-fold higher exposure in females than in males and no accumulation over 28-day duration. The histopathological changes in pancreas and skin was considered to be adverse and the changes in pancreas appeared to be only noted in males and the severity appeared to be not aggravated in association with the 10-fold dose increase, though it was not dose dependent. All toxicities including the histopathological changes appeared to be recoverable after the recovery phase. The MTD was considered to be 500 mg/kg/day for a 28-day repeat dose study.

1.2.2. Studies in Dogs

In an oral maximum tolerated dose study, no mortality or any zanubrutinib related adverse effects were noted in dogs when dosing up to 1,000 mg/kg, with the exception of transient and sporadic incidences of vomiting and slight increases in WBC, NEUT and FIB. The MTD was considered to be higher than 1,000 mg/kg at a single dose level.

In a 14-day oral repeat dose study at 10, 30 or 100 mg/kg/day, no mortality, apparent abnormal changes in body weights, food consumption, ophthalmology, or ECG were noted with the exception of transient and

sporadic incidences of vomiting and slight increases in WBC, NEUT and FIB and decrease in RET at 100 mg/kg/day. Under the condition of this study, the MTD was considered to be higher than 100 mg/kg/day.

In a 28-day oral repeat dose GLP study at 10, 30 or 100 mg/kg/day, no mortality was noted in any treated groups throughout the study. No zanubrutinib related clinical signs were noted with the exception that abnormal stool, vomiting and salivation were noted at ≥ 10 mg/kg/day. No apparent changes in body weights and food consumption were observed. No apparent changes in hematology, serum chemistry, and urinalysis were noted in any treated groups. Increased FIB (37% to 53%) was noted at 30 and 100 mg/kg/day. All of these changes resolved during the recovery phase. A dose-proportional increase in systemic exposure ($AUC_{0\text{-}24h}$) was noted without sex differences or accumulation over 28-day duration. No apparent changes in organ weight or gross lesions were noted throughout the study. Recoverable and non-adverse minimal or mild zanubrutinib-related lymphoid depletion was noted in the spleens at ≥ 10 mg/kg/day. The MTD was considered to be higher than 100 mg/kg/day.

In summary, the toxicity profile of zanubrutinib was well characterized in single and repeat dose studies in dogs up to 28-day duration. No mortality, severe toxicity, or irreversible toxicity was noted in single or repeat dose studies. Zanubrutinib was clinically well tolerated at 100 mg/kg/day in dogs in both 14-day and 28-day repeat dose studies. A dose-proportional increase in systemic exposure ($AUC_{0\text{-}24h}$) was noted without sex differences or accumulation over 28-day duration. The toxicity was dose dependent, reversible, and correlated with the systemic exposure. The MTD was considered to be higher than 100 mg/kg/day for a 28-day repeat dose study.

1.3. Safety Pharmacology

The potential risk of zanubrutinib on QT interval prolongation was assessed using a battery of preclinical studies and a clinical thorough QT study (BGB-3111-106). A GLP compliant hERG assay was conducted. Based on the clinical steady-state, unbound C_{max} of 0.042 μM (total C_{max} 346 ng/mL; plasma protein binding 94.2%) observed at the RP2D of 160 mg BID, there is more than a 200-fold exposure margin compared with the hERG IC50 of 9.11 μM.

No effects on blood pressure, heart rate, or ECG findings, including QT and QTc intervals, were noted in telemetry-instrumented conscious dogs following single doses of zanubrutinib up to 100 mg/kg. In addition, no abnormal changes in ECG or cardiovascular function were noted in 28- and 91-day repeat-dose toxicity studies in dogs at doses up to 100 mg/kg. In these studies, the systemic exposure of zanubrutinib was 10-fold higher than that observed at the human therapeutic dose.

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

1.3.1. Mutagenicity

No mutagenicity was observed in the mini Ames test up to precipitating concentrations (1,000 μg/plate) in the absence and presence of a metabolic activation system.

Refer to the IB for more detailed information on the toxicology of zanubrutinib (BGB-3111 Investigator's Brochure).

1.4. Benefit-Risk Assessment

This is a first-in-human (FIH) study and the side effects of zanubrutinib are unknown.

Zanubrutinib is an investigational product, with safety data available from non-clinical animal studies only. Therefore, patients enrolled in clinical studies with zanubrutinib must be closely monitored by means of reporting adverse events (AEs), recording vital signs and ECGs, and conducting clinical laboratory safety tests of blood and urine.

Clinical experience with existing drugs of the same therapeutic class (BTK inhibitors) suggests that myelosuppression, bleeding diatheses, cardiac arrhythmia, and gastrointestinal disturbances may be observed during multiple dose escalation in patients with cancer.

In this study, patients who have a World Health Organization (WHO)-defined B-lymphoid malignancy, with the exception of Burkitt lymphoma/leukemia, plasma cell myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma and plasmablastic lymphoma will be recruited for the Dose Escalation (Part 1), and patients who have WHO defined CLL/SLL, MCL, WM, FL, marginal zone lymphoma (MZL), DLBCL, or hairy cell leukemia (HCL) will be recruited for the Expansion (Part 2). Other BTK inhibitors in clinical development have shown clinical benefit in these patient populations (Vij, 2014).

1.5. Study Rationale

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines (1996), The Declaration of Helsinki and any applicable regulatory requirements.

This study will evaluate the safety, tolerability, PK and pharmacodynamics, as well as preliminary evidence of the antitumor activity of zanubrutinib. Through its Dose Escalation and Safety, Schedule, and Efficacy Expansion components, it will determine the MTD and the recommended Phase 2 dose (RP2D) for zanubrutinib.

1.5.1. Rationale for Part 1 Starting Dose Selection

Zanubrutinib has demonstrated a very favorable toxicology and safety pharmacology profile in nonclinical experiments. Early clinical development of zanubrutinib will be conducted in patients with advanced cancer.

The safe starting dose for the first administration of zanubrutinib in patients was selected based on relevant regulatory guidance for preclinical development of anticancer drugs, non-clinical pharmacology data, PK data, and toxicological data. Neither STD 10 (one tenth the severely toxic dose in 10% of rodents) in rats nor HNSTD (one-sixth the highest non-severely toxic dose in nonrodents) in dogs were reached in repeat-dose toxicology studies at the high dose, up to 3 months. Based on extrapolation from animal data (ie, one

tenth of the MTD in rats and one-sixth of the MTD in dogs), the human starting dose could be as high as 500 mg/day (detailed calculation is provided in BGB-3111 Investigator's Brochure). Ibrutinib achieved full target inhibition in peripheral blood mononuclear cells (PBMCs) at 2.5 mg/kg in clinic but it was further dose-escalated to much higher dose (12.5 mg/kg). MTD was not reached and 420 mg/ 560 mg (6-8 mg/kg) was selected as its RP2D. Based on mouse PK and pharmacodynamic efficacy model and human PK prediction, it is estimated that zanubrutinib needs to be dosed at around 80 mg/day to achieve complete BTK inhibition in PBMCs in human and 250 mg to achieve the same efficacy as ibrutinib at 560 mg in the clinic. In order to achieve the anticipated therapeutic dose in no more than 4 dose levels and based on the available strength of drug product, 40 mg/day was selected as the safe starting dose for FIH clinical study in cancer patients. The selected FIH dose will be safe and ethical based on the safety profile and the projected efficacy in patients. Human PK predictions suggest that human exposure levels at 40 mg/day should be significantly below exposure levels at MTD in rats and dogs during repeated administration in the toxicology studies.

1.5.2. Rationale for Part 2 Dose Selection

Following the completion of Part 1 of the study in Australia, the Safety Monitoring Committee (SMC) has selected 320 mg once a day (QD) and 160 mg twice a day (BID) doses as the dose regimens to be taken into Part 2 of the study, based on the following rationales:

1. Zanubrutinib was very well-tolerated at all dose levels evaluated.

As of 28 May 2015, the patient enrollment in Part 1 (Dose Escalation) has been completed and 25 patients were enrolled, including 4 patients at the 40 mg QD cohort, 5 patients at the 80 mg QD cohort, 6 patients at the 160 mg QD cohort, 6 patients at the 320 mg QD cohort, and 4 patients at the 160 mg BID cohort. In total, 4 doses of zanubrutinib (40 mg, 80 mg, 160 mg, and 320 mg, QD) and 2 dose regimens of zanubrutinib (320 mg QD versus 160 mg BID) had been evaluated for PK, safety and tolerability including dose limiting toxicities (DLT), pharmacodynamics and preliminary efficacy. In total, 15 patients have received the study treatment for more than 100 days. All 10 patients on 320 mg QD and 160 mg BID cohorts, except 1 patient who came off the study due to progressive disease, have been on treatment for over 2 months, with 4 patients past the 3-month mark. Zanubrutinib was very well tolerated and a MTD was not reached. As of 28 May 2015, only ten Grade 1 and two Grade 2 drug-related adverse events (AEs) were reported for the 25 patients. There were no DLT or drug-related Grade 3 or higher AEs. In addition, no AE of special interest including bleeding or atrial fibrillation has been observed. No relationship between dose level and AEs was apparent.

2. BTK inhibition in PBMCs does not reflect the BTK inhibition in other disease relevant tissues, including lymph node, bone marrow, and spleen.

Preclinical studies using mouse and rat models showed that zanubrutinib achieved potent and sustained BTK inhibition in PBMCs, but much less sustained inhibition in other disease relevant tissues, such as spleen, lymph node and bone marrow (BGB-3111 Investigator's Brochure). Ibrutinib had similar kinetics on BTK inhibition in animal studies. The insufficient BTK inhibition in tissues could lead to reduced efficacy in patients and more profound BTK inhibition may be necessary. The mechanism of this rebound in uninhibited BTK levels at later time point is not completely clear but is likely due to reduced drug levels in the tissues and different protein synthesis rate in PBMCs compared to those in tissues.

Based on these preclinical data, it is hypothesized that BID dosing would provide more sustained target inhibition than QD dosing in disease relevant tissues and could potentially lead to better efficacy and deeper responses in certain disease settings. Cohort 2a of the study will evaluate QD vs BID dosing schedules to examine the difference, if any, of BTK occupancy in lymph node.

3. Zanubrutinib achieved dose-dependent tumor growth inhibition in preclinical xenograft models at doses equivalent to 40 mg to 320 mg in clinic.

Zanubrutinib demonstrated dose-dependent tumor growth inhibition in both Rec-1 MCL and TMD-8 ABC-DLBCL xenograft models at doses ranging from 2.5 mg/kg BID to 25 mg/kg BID (BGB-3111 Investigator's Brochure). No increases in toxicity were observed at the higher doses in these models. These results, in conjunction with the BTK occupancy results, suggest that better efficacy and deeper response might be achieved at higher doses.

4. Data from ibrutinib trial suggested higher doses might provide further clinical benefit.

At the annual meeting of the American Society of Hematology in 2014, it was reported that ibrutinib achieved a better disease control at 840 mg comparing to 420 mg and 560 mg, with or without dexamethasone in multiple myeloma (Vij, 2014). This result supports the hypothesis that more profound BTK inhibition may be necessary to achieve better efficacy in diseases where ibrutinib has limited activity and warrants the testing of a safe and high dose of zanubrutinib in clinic.

1.5.3. Rationale for Inclusion of CLL/SLL, MCL, and WM Patients with Treatment-Naïve Disease

Version 5 of this study provided for the inclusion of patients with CLL/SLL, MCL, or WM who had not received prior treatment for their disease. This provision is based on 1) the highly favorable safety profile of zanubrutinib demonstrated in the Dose Escalation (Part 1) and early Dose Expansion (Part 2) of this study, 2) the emerging data and/ or approvals of ibrutinib in these treatment settings, and 3) in the case of treatment-naïve (TN) MCL, inclusion criteria which define a population for which intensive standard therapy is not an option.

In the Dose Escalation and early Dose Expansion Parts of this study, zanubrutinib has demonstrated a highly favorable safety and activity profile. As of 19 October 2015, seventeen patients with R/R CLL have been enrolled in the ongoing Phase 1 trial and 14 of them have been evaluated the treatment response at least once. Based on the response criteria for CLL, 13 patients achieved partial response/remission (PR) and 1 patient achieved stable disease (SD), with an overall response rate (ORR) of 93% (13/14) in this patient population. In MCL, 8/10 patients achieved at least a PR (2 complete response [CR], 6 PR), and all responding patients remained on therapy at the time of the analysis. In WM, 86% of patients (6/7) have achieved a response, with all responding patients remaining on treatment at the time of the analysis. These data suggest that zanubrutinib is highly active in R/R CLL, MCL, and WM. Treatment has also been well-tolerated. No DLT were encountered in the Dose Escalation（Part 1), and the maximum tolerated dose (MTD) was not reached. As of 19 October 2015, there were no drug-related serious adverse events (SAEs). Only 4 drug-related Grade 3/4 AEs were neutropenia events, which were transient and did not lead to drug discontinuation. Six patients had a baseline history of atrial fibrillation/flutter, but no exacerbation or new event of atrial fibrillation/flutter was reported.

BTK inhibitors, especially ibrutinib, have now been evaluated extensively in TN CLL/SLL. In the most recent published RESONATE-2 results, with a medium follow-up of 18.4 months, ibrutinib demonstrated superiority over chlorambucil as initial treatment of patients over age 65 with CLL/SLL, with a 90% investigator-assessed ORR (9.6% CR/complete remission with incomplete blood count recovery [Cri]) and median progression free survival (PFS) which was not reached at the time of study closure (Burger, 2013). In MCL, a recently reported Phase 3 study suggested that ibrutinib is highly effective in MCL patients who have received only one prior line of therapy, with median PFS was not reached at 24 months (Rule, 2015). This result compares favorably to prior reports of anthracycline/ rituximab-based treatment as initial therapy for older patients with MCL (Kliu-Nelemans, 2012). The TN MCL population identified for inclusion in this study are patients over age 65 with comorbidities which preclude the use of anthracycline-based therapy. In WM, ibrutinib has been approved by US FDA to treat patients with WM regardless of extent of prior therapy.

The above information supports an acceptable risk-benefit balance for inclusion of these patients in and investigation of zanubrutinib in these patient populations.

1.5.4. Rationale for Further Expansion of Cohorts of R/R CLL/SLL, WM, and Non-GCB DLBCL

A preliminary analysis of this ongoing trial has shown that zanubrutinib treatment has been generally well-tolerated and has been associated with durable responses in the range of B-cell malignancies under evaluation. Given the encouraging preliminary activity, additional expansion cohorts, with cohort size between 15 and 40 patients, were added in Version 6. Additional patients will also be added to three of the existing extension cohorts (non-germinal center B-cell (GCB) DLBCL, R/R CLL/SLL, and R/R WM). This will allow a more rigorous description of the safety profile and activity of zanubrutinib in specific B-cell malignancies, thus informing the design of late-stage studies.

Fifty additional patients, for a total of 70, with R/R CLL/SLL will be enrolled into Cohort 2c. The observed response rate in 20 patients is over 90% in the patients enrolled to date, with a lower bound of 95% confidence interval (CI) of approximately 68%. With the addition of 50 patients to this cohort, the lower bound of 95% CI would be approximately 82%, hence, providing a more precise response rate estimate. In addition, the preliminary description of activity in specific molecularly defined subgroups of interest [eg, del(17p) and del(11q)] will be possible, as these are expected to comprise approximately 25-40% of the R/R CLL/SLL population.

Thirty additional patients, for a total of 50, with TN or R/R WM are to be enrolled in Cohort 2f. In a preliminary analysis of the first 20 patients with R/R WM enrolled to date, the major response rate is >80%. With the addition of 30 patients, the lower bound of 95% CI would be increased from approximately 68% to 78%. The additional patients will also enable us to obtain a more accurate estimate of CR or very good partial response (VGPR) rate, which will be important in evaluating the efficacy of zanubrutinib in the R/R WM population.

Similarly, Cohort 2b (non-GCB DLBCL) will be expanded from 20 to 40. The lower bound of 95% CI will be increased from 12% to 17% with 20 additional patients.

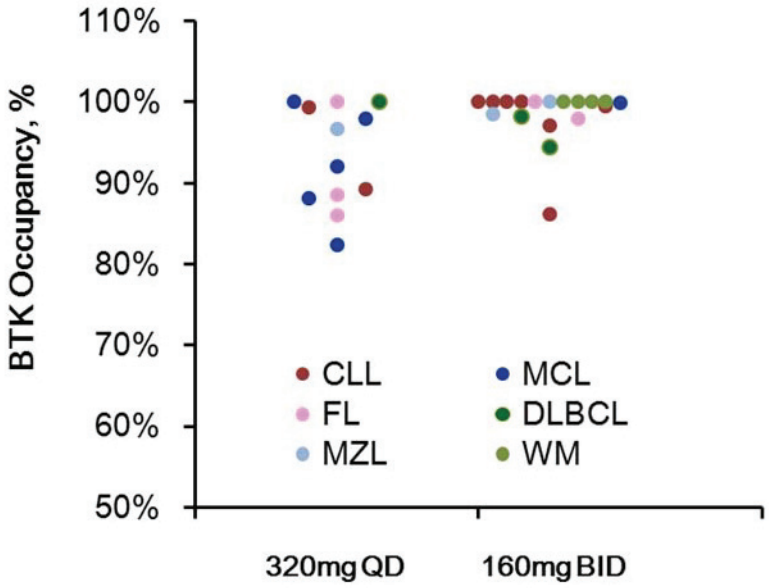
1.5.5. Rationale for Inclusion of Patients with B-cell malignancies who had Prior BTK Therapy in Cohort 2m

BTK inhibitors, such as ibrutinib, are indicated for a number of B-cell malignancies, as an alternative to regimens containing chemoimmunotherapeutic agents. Studies have shown that patients who either progressed, were refractory, or were intolerant to the prior BTK inhibitor therapy side effects, achieved responses when re-treated with another BTK inhibitor (Awan, 2016). Thus, alternative BTK inhibitors with improved efficacy and safety tolerability will allow patients to stay on chemotherapy-free treatment for longer. Zanubrutinib has demonstrated preclinical target inhibition and preliminary clinical safety and efficacy (Tam, 2018) in a variety of B-cell malignancies. Approximately 20 patients who are intolerant to prior BTK inhibitor-related AEs, had disease progression while on a BTK-inhibitor or who are refractory (failed to achieve a PR within 6 months of treatment) to a prior BTK inhibitor therapy, will be enrolled in Cohort 2m to evaluate the safety and efficacy of zanubrutinib in this population.

1.5.6. Rationale for Selection of Twice-Daily Dosing as the Recommended Phase 2 Schedule

Thirty patients from this ongoing study have been evaluated for BTK occupancy in nodal tissue using a fluorescent probe assay on paired lymph node biopsies, 23 patients in Cohorts 2a and 7 patients in other cohorts who consented to optional paired lymph node biopsies. BTK occupancy in lymph nodes (LN) by dose/schedule is shown in Figure 1. Median occupancy was 100% in patients receiving zanubrutinib 160 mg BID (n=18) vs 94% in patients receiving zanubrutinib 320 mg QD (n=12) (p=0.002, Wilcoxon). The proportion of patients with $\geq$ 90% occupancy was 94% (160 mg BID) vs 58% (320 mg QD) (p=0.027, Fisher's exact). Occupancy did not appear to differ amongst histologic subtype. The establishment of sustained BTK occupancy in nodal tissue with BID versus QD dosing supports further evaluation of the 160 mg BID dose of zanubrutinib in this study.

Figure 1. Bruton Tyrosine Kinase Occupancy in Lymph Nodes



Abbreviations; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; WM, Waldenström's macroglobulinaemia

1.5.6.1. Rationale for Removal of Food Restriction

Results from a food effect study showed that zanubrutinib exposure was not altered by high-fat breakfast, and AUC and maximum observed plasma concentration (C_{max}) were increased by 12% and 51%, respectively, with standard breakfast when compared to fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg administered QD in the ongoing Phase 1 study and was not associated with any new safety findings; therefore, zanubrutinib can be administered with or without food.

2. STUDY OBJECTIVES

2.1. Part 1 (Dose Escalation)

2.1.1. Primary Objectives

- To determine the safety and tolerability of zanubrutinib in patients with B-cell malignancies.
- To determine the RP2D and regimen of zanubrutinib when given continuously orally.

2.1.2. Secondary Objectives

- To characterize the PK of zanubrutinib after drug administration.
- To determine the extent of BTK inhibition in PBMCs after treatment with zanubrutinib.
- To describe the preliminary antitumor activity of zanubrutinib.

2.1.3. Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.2. Part 2 (Expansion)

Expansion to determine the safety and efficacy at the RP2D in various Cohorts

2.2.1. Primary Objective

- To further assess the safety and tolerability of zanubrutinib, administered orally either once a day (QD) or twice a day (BID), in patients with specified B-cell malignancies.

2.2.2. Secondary Objectives

- To assess the preliminary antitumor activity of zanubrutinib at RP2D(s) in patients with specific B-cell malignancies.
- To further characterize the PK profile of zanubrutinib.
- To determine the extent of BTK inhibition in PBMCs after treatment with zanubrutinib.

2.2.3. Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY ENDPOINTS

3.1. Part 1 (Dose Escalation)

3.1.1. Primary Endpoints

- The safety of zanubrutinib will be assessed throughout the study by monitoring AEs, SAEs per the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 4.03, physical examination, and laboratory measurements.

- The RP2D and regimen of zanubrutinib will be determined based on PK, BTK inhibition in PBMCs, safety and tolerability, as well as preliminary efficacy.

3.1.2. Secondary Endpoints

- For a single dose profile: area under the plasma concentration time curve from zero to the last measurable concentration (AUC_{last}), AUC, C_{max}, time to maximum observed plasma concentration (t_{max}), terminal half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).
- After steady state ($_{ss}$): $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.
- ORR, complete response rate (CRR), partial response rate (PRR), minimal residual disease (MRD) clearance rate, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).
- BTK inhibition activity of zanubrutinib in PBMCs will be determined via BTK occupancy assay.

3.1.3. Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.2. Part 2 (Expansion)

3.2.1. Primary Endpoint

- The safety and tolerability of zanubrutinib will be further evaluated as described for Part 1.

3.2.2. Secondary Endpoints

- ORR, CRR, PRR, MRD clearance rate, PFS, OS, and DOR.
- The PK profile of zanubrutinib will be further characterized as described for Part 1.
- BTK inhibition activity of zanubrutinib in PBMCs will be determined via BTK occupancy assay.

3.2.3. Exploratory Endpoints

- [redacted]
- [redacted]

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Summary of Study Design

This is a multicenter, Phase 1, open-label, multiple-dose, dose escalation, FIH study. The study includes two parts: a Dose Escalation part (Part 1) and an Expansion part (Part 2).

Part 1 (Dose Escalation) will follow a modified 3+3 dose escalation scheme. The starting dose will be 40 mg/day (QD). The period for DLT assessment is 21 days from first dose of zanubrutinib. Evaluation of a cohort of at least 3 patients completing DLT assessment at any given dose level is required prior to determining the next dose level and dose regimen for the subsequent cohort. The pharmacodynamic effect of zanubrutinib on BTK inhibition will be studied in PBMCs and in LN if available.

The first patient in the first cohort will be admitted to hospital for 24 hours for observation (sentinel patient). Subsequent patients in this cohort will not be dosed until the first patient has been observed for at least 24 hours to exclude unexpected acute toxicity. The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. A SMC will be established for the determination of dose levels to be administered and dose regimen during dose escalation and will utilize the data available from the previous dose levels (Section 11).

In the event that a MTD is not identified due to paucity of DLTs, the dosing regimen used in the Expansion part will be based on PK, pharmacodynamic studies of BTK inhibition in PBMCs, safety, tolerability, and preliminary efficacy.

Part 2 (Expansion) includes Cohorts 2a to 2m (see Section 4.1.2), enrolled in parallel except Cohort 2g, which will be initiated after the enrollment in Cohort 2a is complete. Patients with R/R CLL/SLL will be assigned to either Cohort 2c or Cohort 2e by alternate allocation until Cohort 2c is filled. Patients with R/R WM will be assigned to either Cohort 2d or Cohort 2f by alternate allocation until Cohort 2d is filled. Patients with TN WM will be assigned to Cohort 2f. Cohort 2h and Cohort 2i will not be open to the sites in South Korea.

This study will be considered complete once all patients have either progressed or ceased zanubrutinib due to intolerance, death, or withdrawal from the study.

A flow chart of the study design is presented in Section 14.0, Appendix 4.

4.1.1. Part 1 (Dose Escalation)

The period for DLT assessment is 21 days from the first dose of zanubrutinib.

Evaluation of a cohort of at least 3 patients completing DLT assessment at that dose level and dose regimen is required prior to determining the next dose level for the next cohort.

The study will follow a standard modified 3+3 dose escalation scheme. At least 3 patients will be enrolled into each cohort. Additional patient(s), up to a maximum of 6 patients in total, will be enrolled if more

than 3 have been screened and are eligible for the cohort. The DLT assessment and dose escalation scheme will follow the same principle as stipulated for a standard 3+3 dose escalation design. For example, 3 additional patients will be enrolled if a DLT is observed in 1 of 3 patients; 2 additional patients will be enrolled if a DLT is observed in 1 of 4 patients; and 1 additional patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1 of 6 patients.

The starting dose will be 40 mg/day (once daily; see Section 1.5 for the justification of the starting dose level). The planned Dose Escalation scheme based on currently available data is presented in Table 1; this scheme may change (including exploration of additional dose levels) depending on emerging data during the course of the study. At the highest dose, two dosing schedules, QD vs BID, will be evaluated in parallel for safety. Patients will be assigned to either of the two dosing schedules by alternate allocation. For the BID dosing schedule, patients will take a single administration of zanubrutinib (half of the total daily dose) in the morning of Day 1, followed by repeated drug administration BID (once in the morning and once in the evening with 12 ± 2 hours apart), starting from Day 2. The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the study unjustifiable.

Table 1 Suggested Dose Escalation Scheme

Step	Dose (mg)[1]
-1[2]	20 QD
1	40 QD
2	80 QD
3	160 QD
4a[3]	320 QD
4b[3]	160 BID

1. The actual dose levels and dose regimens administered in each step will depend on the data available from the previous step, as determined by the Safety Monitoring Committee (SMC).
2. In the event that MTD is exceeded at 40 mg/day, the next dose to be explored is 20 mg/day.
3. Two dosing schedules (QD and BID) will be explored in parallel.

As currently planned, if none of the patients in this cohort experience DLT during DLT assessment period, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the SMC.

No additional patients will be treated at a given dose level if 2 or more of the patients in the cohort develop a DLT during DLT assessment period. In this instance, the MTD is considered to have been exceeded.

If the MTD is exceeded, the next lower dose level is planned to be taken forward into Part 2 (Expansion). Depending on the decision of the SMC and on review of available data, an additional intermediate dose level, between the MTD-exceeding dose level and the next lower dose level, may be explored prior to a final decision on the Expansion dose.

In the event that a MTD is not identified due to paucity of DLTs, the Expansion schedule will be based on PK, pharmacodynamic studies of BTK inhibition in PBMCs, safety, tolerability, and preliminary efficacy.

Patients who were enrolled under the QD dosing schedule will have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib (revised per Version 6).

4.1.1.1. Dose-Limiting Toxicity

The period for DLT assessment is 21 days from the first dose of zanubrutinib.

All toxicities or AEs will be graded according to the NCI-CTCAE Version 4.03. A DLT is a toxicity or AE occurring during the DLT assessment period (first 21 days), which is not attributable to a cause unrelated to zanubrutinib (such as disease progression, underlying illness, concurrent illness, or concomitant medication) and meets one of the following criteria:

- Grade 4 neutropenia lasting more than 7 days (even while receiving growth factor support), or Grade ≥ 3 neutropenia with fever.
- Grade 4 thrombocytopenia, or Grade ≥ 3 thrombocytopenia associated with bleeding.
- Any Grade ≥ 2 toxicity requiring dose modification of zanubrutinib, or requiring delay of treatment for ≥ 1 week.
- Any other non-hematologic Grade ≥ 3 event (excluding asymptomatic biochemical abnormalities that are not clinically significant and resolve to Grade 2 or better in < 7 days).
- Any Grade toxicity which in the judgment of the investigator or sponsor requires removal of the patient from the study.

Resumption of zanubrutinib administration for patients experiencing DLTs is permitted, if clinically appropriate, contingent on the return of the DLT to ≤ Grade 1 severity within 14 days and interruption or delay of treatment for no more than 21 days. Resumption of treatment after resolution of a DLT will be at the next lower dose level tested (or 50% lower if the DLT occurs with the first dose level).

If a patient does not receive treatment with at least 75% of the expected dose for reasons other than treatment related toxicity then an additional patient will be enrolled in the cohort.

4.1.1.2. Dose Continuation, Intra-patient Dose Escalation, and Dose De-escalation

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. A SMC will be established for the determination of dose levels to be administered during dose escalation and dose regimens (see Section 11). Before moving to the next dose level, the SMC will review all safety data available to determine whether recruitment to the next cohort should be initiated. At the conclusion of the Dose Escalation (Part 1), the SMC will determine the Expansion (Part 2) dose to be further investigated.

Patients may receive escalated doses of zanubrutinib subsequent to completion of DLT assessment period if they have not experienced clinically significant treatment-related toxicity (Grade 3 or Grade 4 toxicity), and their disease has not progressed. Patients may be permitted to escalate to the higher dose that has been cleared by a subsequent cohort on a case-by-case basis and after discussion between the investigators, sponsor, and medical monitors.

In the event of a DLT, treatment will be stopped and supportive therapy administered as required. If the toxicity resolves or subsides to Grade 0 or Grade 1 (or baseline) within 14 days of the onset of the DLT and the patient is showing clinical benefit in the investigator's opinion, treatment with zanubrutinib may be restarted at the preceding dose level (at the investigator's discretion after discussions with the medical

monitor). If the toxicity does not resolve to Grade 0 or Grade 1 (or baseline) within 14 days of onset, the patient must be withdrawn from the study. Any exception to this must be agreed upon by the investigator and the medical monitor.

4.1.2. Part 2 (Expansion)

All cohorts in the Expansion portion of the study will enroll in parallel with the exception of 2g (MCL patients), which will be initiated after the enrollment of Cohort 2a is complete. Patients with R/R CLL/SLL will be assigned to either Cohort 2c or Cohort 2e by alternate allocation until Cohort 2c is filled. Patients with R/R WM will be assigned to either Cohort 2d or Cohort 2f by alternate allocation until Cohort 2d is filled. Patients with TN WM will be assigned to Cohort 2f. Cohort 2h and Cohort 2i will not be open to the sites in South Korea.

- Cohort 2a will evaluate the RP2D, given on 2 dosing schedules (QD vs BID) in approximately 40 patients with R/R MCL, FL, MZL, or GCB subtype of DLBCL. Patients will be assigned to either the QD dosing schedule that receives the RP2D, or the BID dosing schedule that receives 50% of the RP2D, by alternate allocation based on tumor types. Zanubrutinib safety and efficacy will be assessed. Patients who were enrolled under the QD dosing schedule will have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib (revised per Version 6). Patients in both cohorts will undergo a lymph node biopsy (unless none accessible or judged to be unsafe) at screening stage and before their day 3 dose – ie, either 10-14 or 22-26 hours post dose, depending on assigned schedule - for pharmacodynamic studies of BTK inhibition in lymph nodes, in addition to that in PBMCs.
- Cohort 2b will evaluate the safety and efficacy of zanubrutinib at the RP2D given at the BID dosing schedule (50% of the RP2D) in approximately 40 patients with R/R non-GCB subtype of DLBCL, defined by Hans algorithm.
- Cohort 2c will evaluate the safety and efficacy of zanubrutinib given on the BID dosing schedule (50% of the RP2D) in approximately 70 patients with R/R CLL/SLL.
- Cohort 2d will evaluate the safety and efficacy of zanubrutinib given on the BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R WM.
- Cohort 2e will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R CLL/SLL (revised per Version 6). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2f will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 50 patients with TN or R/R WM (revised per Version 6), requiring treatment per the International Workshop on WM guidelines (Kyle, 2003). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. For United Kingdom (UK) Patients: patients who are TN must be unsuitable for standard chemotherapy.

- Cohort 2g will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with R/R MCL (revised per Version 6). This cohort will be initiated after the enrollment in Cohort 2a is complete. Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2h will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with TN CLL/SLL (Revised per Version 6), requiring treatment per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek, 2008). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2i will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 20 patients with TN MCL, with age ≥ 65 and comorbidity score ≥ 6 using the cumulative illness rating scale (CIRS) (Miller, 1992) (revised per Version 6). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib. This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2j will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a QD or BID dosing schedule (50% of the RP2D) in approximately 10 patients with R/R HCL (revised per Version 6). Patients enrolled to this cohort prior to the activation of Version 6 have the option to be switched to the 160 mg BID dosing schedule of zanubrutinib. Patients enrolled to this cohort after the activation of Version 6 will receive 160 mg BID dosing schedule of zanubrutinib.
- Cohort 2k will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 40 patients with R/R indolent lymphoma, defined as FL, MZL, or mucosa-associated lymphoid tissue (MALT) lymphoma.
- Cohort 2l will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 15 patients with Richter's transformation. Patients with prior BTK inhibitor treatment other than zanubrutinib will be allowed to enroll in this cohort.
- Cohort 2m will evaluate the safety and efficacy of zanubrutinib at the RP2D given on a BID dosing schedule (50% of the RP2D) in approximately 15 patients with R/R B-cell malignancy (otherwise eligible for Cohorts 2a to 2l) who failed to achieve a major response (PR or better) after at least 6 months, had disease progression on prior BTK-inhibitor therapy (ibrutinib, acalabrutinib, zanubrutinib, or other BTK-inhibitor therapy), or discontinued BTK-inhibitor therapy due to an AE. A minimal 7-day washout period is required before initiation of zanubrutinib treatment. All prior BTK inhibitor related AEs must have resolved to Grade 1 or

less.

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. When at least 6 or more patients have been treated with zanubrutinib in an expansion cohort and ≥ 33% of the treated patients experience an event that would meet the definition of a DLT if the event happened during dose escalation (as defined in Section 4.1.1.1 of the protocol), study accrual will be held pending data review by the SMC (see Section 11).

4.2. Selection of Study Population

4.2.1. Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. Aged ≥ 18 years, voluntarily consented to the study.
2. *Part 1 (Dose Escalation):* Relapsed or refractory WHO classification defined B-lymphoid malignancy following at least one line of therapy, with no therapy of higher priority available, with the exception of Burkitt lymphoma/leukemia, plasma cell myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, and plasmablastic lymphoma.
3. *Part 2 (Expansion)*:

- Cohort 2a: R/R WHO-defined MCL, FL, MZL or GCB subtype of DLBCL, with at least one site of biopsiable lymph node.
- Cohort 2b: R/R WHO-defined DLBCL, non-GCB subtype, defined by Hans algorithm. Patients must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype [redacted].
- Cohort 2c: R/R WHO-defined CLL/SLL.
- Cohort 2d: R/R WHO-defined WM.
- Cohort 2e: R/R WHO-defined CLL/SLL on QD or BID dosing schedule.
- Cohort 2f: R/R WHO-defined WM requiring treatment, TN WM, per the International Workshop on WM guidelines (Kyle, 2003). For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2g: R/R WHO-defined MCL.
- Cohort 2h: Previously untreated CLL/SLL requiring treatment per IWCLL guidelines (Hallek, 2008). This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2i: Previously untreated MCL with age ≥ 65 and CIRS ≥ 6 (Miller, 1992). This cohort is not open in South Korea. For UK Patients: patients who are TN must be unsuitable for standard chemotherapy.
- Cohort 2j: R/R WHO-defined HCL.

- Cohort 2k: R/R WHO-defined indolent lymphoma (inclusive of FL, MZL, and MALT lymphoma).
- Cohort 2l: Histologically-confirmed Richter's transformation of CLL/SLL. Patients who previously received a BTK inhibitor other than zanubrutinib are allowed. Patients to be enrolled must have histologic confirmation of Richter's transformation prior to enrollment.
- Cohort 2m: R/R B-cell malignancy (otherwise eligible for Cohort 2a to 2l) who failed to achieve a major response (PR or better) after at least 6 months, had disease progression on prior BTK-inhibitor therapy (ibrutinib, acalabrutinib, zanubrutinib, or other BTK-inhibitor therapy), or discontinued BTK-inhibitor therapy due to an AE. A minimal 7-day washout period is required before initiation of zanubrutinib treatment. All prior BTK inhibitor related AEs must have resolved to Grade 1 or less.

4. Requirement for treatment in the opinion of the investigator.
5. Eastern Cooperative Oncology Group (ECOG) Performance status of 0-2.
6. Adequate hematologic function, as defined by neutrophils $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L; patients with neutrophils $< 1.0 \times 10^9$/L due to marrow infiltration are allowed to receive growth factors to bring pre-treatment neutrophils to $\geq 1.0 \times 10^9$/L; patients with platelets $< 50 \times 10^9$/L due to marrow infiltration are allowed to receive platelet transfusion to bring pre-treatment platelets to $\geq 50 \times 10^9$/L.
7. Adequate renal function, as defined by creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation/CKD-EPI equation or as measured by nuclear medicine scan or 24 hour urine collection).
8. Adequate liver function, as defined by aspartate aminotransferase (AST) and ALT ≤ 3 x upper limit of normal (ULN), and bilirubin ≤ 1.5 x ULN (unless documented Gilbert's syndrome).
9. International normalized ratio (INR) ≤ 1.5 and APTT ≤ 1.5 x ULN.
10. Female patients of childbearing potential and non-sterile males must practice at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, intrauterine device (IUD) or hormonal contraceptive initiated at least 3 months prior to first dose of study drug.

- Female patients of childbearing potential and non-sterile males must practice highly effective methods of birth control initiated at least 3 months prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug. These methods include the following:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
        - Oral, intravaginal or transdermal
    - Progestogen-only hormonal contraception associated with the inhibition of ovulation

        - Oral, injectable, implantable
    - An IUD
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle.

- 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.

11. Male patients must not donate sperm from initial study drug administration, until 90 days after drug discontinuation.

4.2.2. Exclusion Criteria

Patients will not be entered in the study for any of the following reasons:

1. Current central nervous system (CNS) involvement by lymphoma or leukemia.
2. Current histologically transformed disease except patients in Cohort 2l.
3. Prior BTK inhibitor treatment except patients in Cohort 2l and Cohort 2m.
4. Allogeneic stem cell transplantation within 6 months or has active graft-versus-host disease (GVHD) requiring ongoing immunosuppression.
5. Receipt of the following treatment prior to first dose of zanubrutinib: corticosteroids given with antineoplastic intent within 7 days, chemotherapy or radiotherapy within 2 weeks, monoclonal antibody within 4 weeks.
6. Not recovered from toxicity of any prior chemotherapy to Grade ≤ 1.
7. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated *in-situ* carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
8. Uncontrolled systemic infection requiring parenteral antimicrobial therapy.
9. Major surgery in the past 4 weeks.
10. Known infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus

(HBV) DNA is undetectable.

b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.

11. Cardiovascular disease resulting in New York Heart Association function status of ≥ 3.
12. QTcF > 480 msecs based on the Fridericia's formula or other significant ECG abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).
13. Significant active renal, neurologic, psychiatric, hepatic or endocrinologic disease that in the investigator's opinion would adversely impact on his/her participating in the study.
14. Inability to comply with study procedures.
15. On medications which are strong CYP3A inhibitors or strong CYP3A inducers (see Section 6.2).
16. Pregnant and breast-feeding women are excluded from the study.

4.2.3. Other Eligibility Criteria Considerations

To assess any potential impact on patient eligibility with regard to safety, the investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study (BGB-3111 Investigator's Brochure).

4.3. Patient Completion and Withdrawal

4.3.1.1. Patient Completion

Patients in Part 1 (Dose Escalation) will be considered complete if he/she has a valid PK profile (including data from Week 2 Day 1) and has not withdrawn from the study prior to completing DLT period (21 days from first dose of zanubrutinib) or experiencing a DLT.

Patients in Part 2 (Expansion) will be considered complete if he/she has not withdrawn from the study prior to completing 1 full cycle of study treatment.

Incomplete patients who drop out or are withdrawn for any reason may trigger additional patient enrollment (ie, to fulfill the necessary number of patients with adequate data in a dose escalation cohort) after due consideration from sponsor and SMC.

4.3.1.2. Patient Withdrawal and End of Study

This section is intended to clarify reasons for patient withdrawal from the study; study drug discontinuation is described in Section 5.5.6.

A patient should continue on the study until the study ends or there a reason for the patient to withdraw from the study.

A patient may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the patient from participating in this study at any time. If a patient is prematurely discontinued from participation in the study for any reason, the investigator must make every

effort to perform the Safety Follow-Up visit (see Section 7.8). These data will be recorded as they comprise an essential evaluation that needs to be done prior to discharging any patient from the study.

Patients that withdraw from the study should immediately discontinue taking any study drug.

Patients must be discontinued from the study for any one of the following reasons, at which point they will be considered to have reached the end of study:

- Withdrawal of consent by the patient
- Discontinuation of the patient on the study by the investigator
- Discontinuation or closure of the study by the sponsor
- Lack of compliance with the study and/or study procedures (eg, administration instructions, study visits)
- Significant deviation from the protocol by the investigator without the consent of the sponsor
- Start of alternative anticancer therapy to treat the condition initially being evaluated in this study

Patients may choose to come off study for reasons other than those listed above (ie, for adverse events), but are not required to do so.

In the event that a patient is discontinued from the study at any time for reasons relating to an AE (as defined in Section 9.1), the procedures stated in Section 9.0 must be followed.

In addition to the end of treatment assessments, if a DLT occurs, the investigator will obtain, when possible, a 4-mL blood sample for analysis of plasma zanubrutinib concentration as soon as possible (see Section 7.5.1).

4.4. Study Duration

Patients will continue on study until one of the events listed in Section 4.3 occurs, which includes discontinuation or closure of the study. Closure of the study is expected to occur approximately 5 years after the first patient has been enrolled. Patients still benefitting from study treatment at the time of Study Closure will be provided zanubrutinib in an extension study.

5. STUDY TREATMENTS

5.1. Treatment Assignment

Patients will be identified by a patient number. Each patient enrolled in this study will receive a unique patient number which will be assigned when the patient is screened or enrolled in the study. Each patient receiving zanubrutinib will also receive a treatment allocation number. Patient and treatment numbers will be assigned in chronological order starting with the lowest number. Once a patient number and treatment number have been assigned to a patient, it cannot be reassigned to any other patient.

5.2. Study Treatment Preparation and Dispensation

5.2.1. Packaging and Labeling

The capsule supplies of zanubrutinib will be provided in a child-resistant closure and be open-labeled with space to enter the patient number and name of investigator. The label will also include content and quantity of zanubrutinib, protocol number, batch number, administration instructions, storage conditions, and cautions.

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

5.2.2. Handling and Storage

A manual process 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 acknowledgment 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 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.

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).

5.2.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

5.2.4. 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.

5.3. Dosage and Administration

Patients will receive zanubrutinib as 20 mg blue opaque capsules (size 3), or 80 mg white opaque capsules (size 0), depending on the dose level.

The study drug will be taken QD or BID. For the BID cohort, patients will take repeated drug administration twice daily (once in the morning and once in the evening with 12 ± 2 hours apart), starting from Day 1. If the evening dose is not taken within this time window this should be documented in the patient diary including the actual time of the administration and a comment added to the electronic case report form (eCRF) documenting this.

Patients will be advised that if a dose of the study drug is not taken at the scheduled time, they should take the missed dose as soon as they remember and return to the normal schedule for the next dose. Patients should skip the missed dose if it is 8 hours or less to the next scheduled dose. An extra dose of the study drug should not be taken to make up for the missed dose.

The patients will continue to take the study drug until occurrence of unacceptable toxicities, disease progression, withdrawal of consent, investigator discretion, or a treatment delay for more than 28 days for unresolved toxicity. Exceptions to the 28-day delay must be agreed upon by the investigator and the medical monitor. Interruption of zanubrutinib for up to 4 weeks can be permitted to allow short term use of the prohibited medications if agreed by the investigator and the medical monitor. Changes may be made to the dose levels and/or the schedule of administration based on the results of the PK analysis.

For management of toxicity refer to Section 9.0.

5.4. Treatment of Study Drug Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any AE or SAE criterion must be reported in the appropriate timeframe and documented as clinical sequelae to an overdose.There is no specific antidote for zanubrutinib. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

5.5. Special Precautions

5.5.1. Occupational Safety

Study drug is not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from the sponsor.

5.5.2. Tumor Lysis Syndrome

Patients with a high tumor burden (WBC $\geq 25 \times 10^9$/L or bulky lymphadenopathy) should receive prophylaxis for tumor lysis syndrome (TLS) prior to the initiation of treatment. These patients must be well hydrated. It is desirable to maintain a fluid intake of approximately 3 liters per day, 1-2 days before the first dose of zanubrutinib. All such patients with high tumor burden must be treated with allopurinol

(≥300 mg by mouth [PO] QD) or a suitable alternative treatment starting 12-24 hours prior to the first dose of zanubrutinib. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each dosing, if deemed appropriate by the investigator.

5.5.3. Drug Dose Modification

Certain circumstances or AEs will require holding study drug (Section 5.5.4), reducing the dose of the drug (Section 5.5.3), permanently discontinuing study drug (Section 5.5.6), or some combination of all three.

5.5.4. Dose Holds

Certain circumstances or adverse events will require holding study drug, which can later be restarted. A drug hold may also necessitate reducing the dose upon restart (Section 5.5.5).

Study drug may be 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 more than 28 days, then written approval must be obtained from the sponsor medical monitor.

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, if not otherwise specified in the guidance below 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.

5.5.4.1. Dose Holds for Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions:

- Grade 4 neutropenia related to zanubrutinib lasting >10 days despite the use of growth factors
- ≥ Grade 3 febrile neutropenia related to zanubrutinib
- Grade 4 thrombocytopenia related to zanubrutinib lasting >10 days
- ≥ Grade 3 thrombocytopenia associated with significant bleeding

5.5.4.2. Dose Holds for Non-Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions:

- All non-cardiac, non-hematological toxicities ≥ Grade 3 (other than hypertension adequately controlled with oral medication or asymptomatic lab abnormalities unrelated to liver or renal dysfunction) suspected to be **related** to study drug treatment

Study drug may be restarted upon recovery to ≤ Grade 1 or baseline, but the dose may need to be reduced (Section 5.5.5.2).

Zanubrutinib should be held for any ≥ Grade 3 bleeding. The drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in GI bleed) and the risk of a re-bleed is deemed acceptable.

5.5.4.3. Dose Holds for Cardiac Toxicity

Dosing will be held for individual patients under any of the following conditions:

- ≥ Grade 3 cardiac toxicities, including arrhythmias and QTc prolongation other than atrial fibrillation, suspected to be **related** to study drug treatment.

Study drug may be restarted upon recovery and/or appropriate treatment instituted, but the dose may need to be reduced (Section 5.5.5.3).

5.5.4.4. Dose Holds for Surgeries and Procedures

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

5.5.4.5. Restarting Study Drug

If dose was held for reasons not otherwise specified in Section 5.5.4 (ie, patient error), drug may be restarted immediately at full dose as long the patient is fit for dosing in the opinion of the treating physician.

5.5.5. Dose Reductions

The guidelines set forth in Table 2 should be followed for events requiring a dose reduction. For patients who are at 160 mg, one dose level reduction to 80 mg QD is allowed. For patients who are at 40 and 80 mg QD, no dose reduction is allowed.

Table 2 Zanubrutinib Dose Reduction Steps

Dose Level	Zanubrutinib Dose	
0 = starting dose	320 mg QD	160 mg BID
-1 dose level	160 mg QD	80 mg BID
-2 dose level	80 mg QD	80 mg QD

5.5.5.1. Dose Reductions for Hematologic Toxicity

Hematological AEs requiring a dose hold (Section 5.5.4.1) that lasted over 7 days require that patients restart at dose level -1. If the same event reoccurs, patients will restart at one dose level lower. Maximum 2 dose reductions are allowed.

5.5.5.2. Dose Reductions for Non-Hematologic Toxicity (Non-Cardiac)

Non-Hematological AEs requiring a dose hold (Section 5.5.4.2) will be restarted at dose level -1. For events that recur at ≥ Grade 3, drug will be restarted at level -2. If the event recurs at ≥ Grade 3 at level -2, the patient will be discontinued from study treatment.

5.5.5.3. Dose Reductions for Cardiac Toxicities

Cardiac toxicities requiring a dose hold (Section 5.5.4.3) will be restarted at dose level -2, with the following exceptions:

- Atrial fibrillation (≥ Grade 3), reinstatement of study drug may be at dose level -1, per investigator discretion. If atrial fibrillation recurs after reduction to dose level-1, study retreatment will be reduced to dose level -2.

If the cardiac toxicity recurs, study drug will be discontinued permanently.

5.5.6. Discontinuation from Study Treatment

Patients should discontinue study treatment for the following:

- Discontinuation of zanubrutinib by the sponsor
- Withdrawal from the study (see Section 4.3.1.2).
- Pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Intercurrent illness that compromises the patient's ability to participate in the study
- Unequivocal progression. Note that patients with disease progression may continue study drug treatment if they are benefiting from the treatment in the judgment of the investigators, with approval from the medical monitor.
- Need for prohibited medication
- Start of alternative anticancer therapy to treat the condition initially being evaluated in this study, or start of therapy for secondary malignancy that would interfere with assessment of zanubrutinib safety and efficacy
- Study drug interruption > 4 weeks (unless agreed by the investigator and the medical monitor)
- Adverse events including:
    - Hematological toxicity requiring dose reduction below dose level -2
    - Recurrent ≥ Grade 3 non-hematological toxicity at dose level -2
    - Recurrent cardiac toxicity (with some exception, see Section 5.5.5.3)
    - Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding
    - Any significant AE that compromises the patient's ability to participate in the study
- Zanubrutinib should be permanently discontinued for any intracranial hemorrhage

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

6. PRIOR AND CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Prior Therapy

Medications taken within 4 weeks before randomization and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, will be recorded.

6.2. Concomitant Therapy

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

6.2.1. Permitted Medications

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for indications not associated with the disease under study

  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 conditions not associated with the disease under study (eg, to treat a flare of chronic obstructive pulmonary disease). Chronic systemic corticosteroid use is not permitted, except for adrenal replacement – consult the medical monitor for this situation.
- Therapy to reduce symptoms of disease per standard of care and institutional guidelines
- Bisphosphonates can be coadministered with zanubrutinib.
- 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 of opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

6.2.2. Prohibited Medications

Patients should not receive other anticancer therapy (cytotoxic, biologic, or immunotherapy) 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. Localized anticancer therapy to treat conditions allowed by the inclusion/exclusion criteria are acceptable after approval of the medical monitor.

6.2.3. CYP-Inhibiting/Inducing Drugs

A clinical drug-drug interaction study with zanubrutinib is currently ongoing. Based on available nonclinical metabolism data, zanubrutinib is primarily metabolized by CYP3A. Avoid concomitant administration of zanubrutinib with strong CYP3A inhibitors or strong CYP3A inducers (refer to Appendix 5 for a list of these medications). Star fruit, pomegranate, and grapefruit and their juices and Seville oranges should be avoided, as they may affect the metabolism of zanubrutinib. For short-term use (treatment for ≤ 7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting

zanubrutinib therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations.

Based on in vitro data, zanubrutinib is a moderate inhibitor of the human isoenzymes CYP2C8, CYP2C9, and CYP2C19. Drugs that are primarily metabolized by these isoenzymes and with a narrow therapeutic index should be used with caution when administering zanubrutinib, with monitoring of drug concentrations where appropriate (refer to Appendix 6).

Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

7. STUDY PROCEDURES

The schedule of assessment is presented in Appendix 7, Table 5.

A signed, written informed consent must be obtained prior to Screening assessments and before any study-specific assessments are initiated. The study-specific assessments and procedures are shown in the study assessments and procedures schedule in Appendix 7, Table 5. The PK and pharmacodynamic sampling time points are presented in Table 6 and Table 7.

7.1. Demographic and Baseline Assessments

Demographic data will include date of birth, race, height (in cm), body weight (in kg), and body mass index (BMI; in kg/m^2). For height and weight measurements, the patient will be allowed to wear indoor daytime clothing with no shoes. This data will be captured in the eCRF and database.

Having given consent, patients will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the criteria listed in Section 4.2. Screening assessments will be completed within 28 days prior to the first dose of the study drug. Screening assessments completed within 72 hours of administration can be used as Day 1 assessments as indicated in Appendix 7,Table 5.

These data will be captured in the source documents. Any results falling outside the normal range will be repeated at the discretion of the investigator.

7.2. Safety Assessments

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Appendix 7, Table 5.

7.2.1. Physical Examination, Vital Signs, and B Symptoms

A complete or targeted physical examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified in Appendix 7, Table 5.

Complete physical examination includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes,

liver, and spleen), and those systems associated with clinical signs/symptoms. B symptoms include unexplained weight loss > 10% over previous 6 months, fever (> 38°C), and/or drenching night sweats.

7.2.2. Electrocardiogram

Perform a single 12-lead ECG in triplicate at Screening and at the treatment completion/early termination visit. After Week 9, this test will be performed as clinically indicated. Patients should be in the semi-recumbent or supine position.

ECGs will be obtained at the time points specified in Appendix 7, Table 5 and Table 6.

Significant QTc prolongation will be defined as an interval QTcF > 500 msec or an interval which increases by ≥ 60 msec over baseline. (Note: For patients enrolled under protocol version 3 or earlier, in which there was no restriction on QTc at study entry, QTc prolongation will be defined only by an increase of ≥ 60 msec over baseline.) Either of these conditions should be documented on two or more ECG tracings separated by at least 5 minutes. The ECG tracing should be examined and a manual measurement by a trained physician should be performed to assess the accuracy of the equipment being used.

If a patient has significant QTc prolongation：

- He/she will suspend investigational product administration.
- The patient will be medically assessed, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 msec of baseline.
- The medical monitor will be consulted prior to administering further doses or re-challenging.
- The medical monitor will be consulted prior to administering higher doses.

7.2.3. Adverse Events

All AEs and SAEs, regardless of the relationship to the study drug, will be collected from patient consenting, until 28 days after last dose of zanubrutinib. All treatment-related AEs and serious AEs (SAEs) will be followed until resolution or stabilization.

Throughout the study, the study center personnel will be monitoring AEs. AEs and toxicities will be graded according to NCI-CTCAE, Version 4.03.

7.2.4. Concomitant Medications

The investigator must be informed as soon as possible about any medications taken from the time of Screening until the patient is discharged from the study.

7.3. Efficacy Assessments

Overall response to study drug for each patient will be assessed using disease-standard criteria as specified in Appendix 3 and response assessments should be reviewed and updated according to the most recent version of the protocol. For purposes of evaluation by independent review, IgM-only response for WM will also be evaluated. For MCL, CT-based response will also be evaluated. Depending on disease, this

assessment will incorporate several components listed in Section 7, including imaging, physical exam, laboratory evaluations, vital signs, bone marrow/ tumor biopsy evaluation, and B symptoms.

Response should be assessed against baseline unless otherwise noted by Appendix 3. Overall disease response will be used in assessments of study efficacy (Section 10.2).

Responses will be assessed every 12 weeks (end of Weeks 12, 24, 36 and 48) during the first year of treatment. After Week 52, appropriate imaging for response assessment should be conducted every 24 weeks (beginning Week 76) or when a significant change in response is suspected (progressive disease [PD] or upgrade of response). For patients with MCL, after Week 52, appropriate imaging for response assessment should be conducted every 12 weeks starting from Week 64 (end of Weeks 64, 76, 88, 100) and every 24 weeks thereafter from Week 100 or when a significant change in response is suspected (PD or upgrade of response).

Unscheduled visits with assessments sufficient to determine a change in overall response in the patient (i.e. unscheduled CT scans and labs, IgM-based change response between scheduled efficacy assessments for WM patients) should have an overall efficacy response assessment completed and all data entered into EDC.

Pseudo-progression due to tumor flare or other causes may occur with BTK inhibitor treatment. Progression should be confirmed and unequivocal before an assessment of progressive disease is made.

For patients with new disease symptoms, every effort should be made to obtain and document objective evidence of disease progression according to the disease-specific response criteria (Appendix 3). Of note, progressive disease cannot be determined solely by the presence of B symptoms. Disease progression due to new symptomatic disease must be accompanied by objective evidence (e.g. imaging, laboratory value, biopsy or bone marrow histology) consistent with the disease and associated response criteria for progression. For example, a patient with WM, in the absence of IgM increase or other objective measures of disease progression, new B-symptoms alone should not be the sole reason to discontinue a patient from study treatment.

Imaging scans and associated data may be collected centrally for independent efficacy review.

7.3.1. Computed Tomography

Computerized tomography (CT) scan with contrast or a CT scan of diagnostic quality performed as part of positron emission tomography (PET)/CT and is required at screening, throughout the study, and at disease progression (Appendix 7, Table 5). The frequency of CT scans for patients with HCL could follow institutional standard after Week 52.

At baseline, PET scan or an integrated PET/CT may be performed at investigator discretion. Complete response should be confirmed by PET scan or an integrated PET/CT for patients who had PET-avid disease during Screening, where standardized response criteria for that disease require such an assessment for CR confirmation. CT scans must encompass neck, chest, abdomen and pelvis and include oral and intravenous contrast. A CT scan of diagnostic quality performed as part of PET/CT is acceptable, provided that bidimensional nodal and liver/spleen measurements can be made. Magnetic resonance imaging (MRI) may be used in place of CT in clinical scenarios where anatomical location of an evaluable

lesion (such as soft tissue) precludes accurate measurement by CT. If the patient has no assessable disease by CT at baseline (eg, WM without nodal enlargement) at study entry, repeat scans are not required. The CT scan will be used for disease assessment by the investigator at each study center.

For scheduled scans, if a scan has been done within 4 weeks of the scheduled time, it does not need to be repeated. For patients who discontinue early, a CT scan will be performed at the discontinuation visit if the previous scan was more than 3 months prior. Patients with confirmed CR may choose to either have scans performed every 24 weeks or as specified in the schedule, whichever is less frequent. The Week 48 scan is always required, regardless of patient status.

7.3.2. PET and integrated PET/CT

At baseline, PET scan or an integrated PET/CT may be performed at investigator discretion. PET/CT scan may be used in place of CT scan (Section 7.3.1) throughout the study provided the CT component is of diagnostic quality.

Complete response should be confirmed by PET scan or an integrated PET/CT for patients who had PET-avid disease during Screening, where standardized response criteria for that disease require such an assessment for CR confirmation.

7.3.3. Bone Marrow Evaluation

A bone marrow examination must be performed at Screening for all patients and within 7 days of the end of Week 12 for patients with baseline marrow involvement. Thereafter, bone marrow examination is only required for patients with baseline marrow involvement who need bone marrow examination to confirm CR. Patients who are otherwise complete responders, but are positive for bone marrow involvement, should have their bone marrow rechecked as clinically indicated, but at a minimum of at least once per year until CR is confirmed.

For scheduled bone marrow evaluations, if one has been done within 4 weeks of the scheduled time, it does not need to be repeated.

The bone marrow biopsy and aspiration are expected from WM patients, when consented, for the mutation analysis, including but not limited to MYD88 and CXCR4. For the WM patients who have been enrolled, the bone marrow samples can be retrieved after they sign the new consent form. The bone marrow samples could be used for research corollary studies, when consented. Only one bone marrow sample for each patient will be used for the mutation analysis.

A bone marrow/ tumor biopsy confirmation is necessary for patients suspected to have disease transformation. For patients with CLL, a blood test for confirmation of disease transformation is necessary. Transformation of WM to large cell lymphoma (Richter's transformation) is considered as progressive disease.

7.4. Laboratory Assessments

Laboratory assessments should be performed at a local certified laboratory on Day 1 before the study drug administration. Laboratory assessments need not be repeated on Day 1 if these assessments were

completed for screening within 72 hours of the first administration. Required assessments are listed in Appendix 2.

Clinical chemistry, hematology, coagulation, urinalysis, and immunoglobulin assessment (including cryoglobulin and immunofixation, if clinically indicated) and serum electrophoresis protein globulins (EPG) will be performed at the time points specified in Appendix 7, Table 5. For WM patients, β2-microglobulin value at screening will also be collected - a value from standard of care assessment within 90 days of W1D1 is acceptable.

In the event of neutropenia (absolute neutrophil count [ANC] < 1000/mm^3), thrombocytopenia (platelets < 50,000/mm^3), or Grade 3 clinical chemistry toxicity, the relevant assessments will be conducted as frequent as physician feels needed until toxicity resolves to ≤ Grade 2 toxicity. If warranted, additional testing can also be done, or the relevant tests done more frequently in accordance with institutional guidelines. All patients, who have any Grade 3 or Grade 4 laboratory abnormalities at withdrawal from the study, must be followed up until they have returned to Grade 1 or Grade 2, unless these are not likely to improve due to the underlying disease.

On routine urinalysis, if urine protein is ≥ 2+ by dipstick and clinically significant, a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine will be obtained. If urine protein is > 2 g/24 hours, the investigational product administration will be interrupted until it returns to ≤ 2 g/24 hours. If urine protein is ≤ 2 g/24 hours, further clinical evaluation and/or more frequent testing may be performed as clinically indicated. A random urine protein to creatinine ratio can serve as a reliable surrogate for the 24-hour urine protein when following patients with urine protein of ≤ 2 g, documented by a 24-hour urine collection. In such cases, the 24-hour urine for total protein should be repeated only if a clinically significant increase is observed in the random urine protein to creatinine ratio. After Week 9, this test will be performed as clinically indicated.

Serum electrophoresis protein globulins (EPG) should be tested during screening for all WM patients, and if a paraprotein is present, it should be repeated on all subsequent immunoglobulin assessments.

7.4.1. Hepatitis B and C and HIV Testing

Hepatitis B/C serologic markers and/or viral load will be tested at Screening.

HBV

The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as HBV DNA by polymerase chain reaction (PCR) if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible. Patients who are HBsAg-negative, HBcAb-positive and HBV DNA-negative must undergo monthly HBV DNA screening by PCR.

HCV

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

HIV

Patients with known infection with HIV are excluded from the study.

Guidance for HBV and HCV

The following text represents guidance to sites, but sites are free to follow local practice including the use of site specific testing sensitivity, as applicable.

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 stopped and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped and antiviral therapy initiated. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B.

Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis C.

Table 3 below, shows how the results for HBV/HCV and HBV/HCV testing at screening relate to inclusion and exclusion criteria.

Table 3 Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by PCR)

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

Abbreviations: HBsAg: hepatitis B surface antigen; HBcAb: hepatitis B core antibody; HBV: hepatitis B virus; HCV: hepatitis C virus; PCR: polymerase chain reaction.

7.4.2. Pregnancy Testing

A serum pregnancy test will be performed at Screening and a urine pregnancy test at the time points specified in Appendix 7, Table 5 in women of childbearing potential. Any female patient who is pregnant will not be eligible for the study (see Section 4.2). A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

The results of pregnancy tests will not be recorded in the database.

Reporting requirements for pregnancy are given in Section 9.5.

7.5. Pharmacokinetics

Blood will be collected to describe the PK profile of zanubrutinib and for a preliminary analysis of major metabolites if needed.

The maximum total amount of blood taken for the PK analysis will be approximately 72 mL. These samples will be collected at the time points presented in Table 6 , Table 7, and Table 8. Should a patient undergo an intra-patient dose escalation, additional PK samples (2-4mL) will be collected (in addition to those listed in Table 6 and Table 7). At selected clinical sites, patients receiving study treatment in the form of a new drug product supply (e.g. a new manufacturer) will be eligible to participate in an optional intensive PK sampling study. The PK blood samples will be collected over an 8- hour period according to the schedule in Table 8, as soon as feasible. Frozen plasma samples should be shipped as soon as possible after collection since exposure will be monitored while the study is ongoing.

7.5.1. Pharmacokinetic Blood Samples

Cannulation for blood sampling for PK will be performed. Blood will be collected via the intravenous cannula pre-dose and at the time points specified in Table 6**,** Table 7, and Table 8. The actual time each sample was collected and the dosing time prior to the PK sampling (e.g, W1D1 and W2D1) will be captured to the nearest minute in the eCRF and recorded in the database.

Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Study Manual.

In addition to the post-study assessments, if a DLT occurs, the investigator will obtain, when possible, a 4-mL blood sample for analysis of plasma zanubrutinib concentration as soon as possible.

Should a drug-drug-interaction (DDI) between zanubrutinib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.

Samples will be shipped to the central laboratory where all samples will be analyzed for plasma zanubrutinib concentrations using a validated method.

7.6. Pharmacodynamics

BTK occupancy in PBMCs and LN biopsy will be determined and used as direct pharmacodynamic biomarker for BTK inhibition. PBMC and tissue collection for pharmacodynamic biomarker analysis is complete as of Version 7.

7.6.1. PBMC Preparation

Blood samples (8 mL) for pharmacodynamic analysis will be collected into plastic potassium (ethylenediaminetetraacetic acid [EDTA]) collection tubes immediately following PK blood sampling at the time points specified in Table 6 and Table 7. PBMCs will be prepared using the peripheral blood mononuclear cell preparation kit provided by the sponsor. PBMC samples will be immediately frozen in a freezer at or below -70°C.

7.6.2. Pharmacodynamic Tissue Samples Preparation

This is for Expansion cohort only. This is mandatory for Cohort 2a and optional for Cohorts 2b to 2j. Two needle cores are collected at Screening, and repeated on Week 1 Day 3, within 2 hours prior to zanubrutinib administration on that day. Needle biopsy samples will be immediately frozen in a freezer at or below -70°C. The pharmacodynamic tissue sampling will be stopped when Version 6 is active.

7.6.3. Sample Shipment and Analysis

Samples must remain frozen in a box with dry ice during shipping. Samples will be shipped to the central laboratory where samples will be analyzed for BTK occupancy using a validated method.

7.7. Other Assessments

Correlative blood will be collected if the site has the access to central laboratory for platelet functional assay and host immunity analysis.

In-vitro platelet function assessments will be performed using light transmission aggregometry, thromboelastrograph and phosphoprotein studies on patients enrolled in Part 1. Thirty mL of blood in citrate will be collected during the screening period and on Week 5 Day 1, and transported to the central laboratory within 3 hours according to the instructions in the laboratory instructions manual.

For all patients enrolled in Part 1 and approximately 7 CLL patients enrolled in Part 2 at sites located in Melbourne, changes in host immunity will be assessed by an established suite of flow cytometry / cytokine panel assays. At the specified time points (Appendix 7, Table 5), 30 mL of blood in ACD will be collected and transported at room temperature to the central laboratory within 8 hours according to the instructions in the laboratory instructions manual.

7.7.1. Plasmapheresis

If a patient requires plasmapheresis, a blood sample for PK analysis should be obtained within 2 hours after the procedure has been performed.

7.7.2. Tumor Type at Baseline

DLBCL patients must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype [redacted], either prior to enrollment or during/after the study treatment. Either a formalin-fixed, paraffin-embedded block with tumor tissue (preferred) or 10 to 15 unstained slides must be sent to the central laboratory to confirm the DLBCL subtype [redacted]. Patients to be enrolled in Cohort 2l must have histologic confirmation of Richter's transformation prior to enrollment. Patients enrolled to all other cohorts should have archival tumor tissues available or agree to a tumor biopsy [redacted].

7.7.3. Resistance Markers

Patients who have disease relapse at any time will be asked for a blood sample and asked to undergo re-biopsies of representative tumor sites to obtain samples for studying mechanisms of resistance. These studies may include phosphoprotein analysis of relevant pathways, whole exome or genome sequencing, and assessments of RNA expression. To achieve these goals, at disease progression, CLL patients will be

asked for a peripheral blood sample, WM patients will be asked for a bone marrow aspirate, and patients from other indications will be asked to undergo a tissue biopsy of representative tumor sites. If feasible, samples collected for PD confirmation may be used for biomarker testing in lieu of requesting additional marrow and biopsy samples from patients. For non-CLL patients, while bone marrow collection or tumor tissue biopsy is preferred, peripheral blood samples are acceptable if marrow or biopsies are not accessible.

7.7.4. Chronic Lymphocytic Leukemia Prognostic Labs

Patients with CLL should have a blood sample sent at screening for cytogenetic analysis, including: immunoglobulin variable region heavy chain (IgHV) mutational status and interphase fluorescent in situ hybridization (FISH) for chromosomal abnormalities including 17p-, 11q-, 13q-, and +12. These labs should be done locally and are otherwise considered optional.

7.7.5. Minimal Residual Disease Samples

If available at a site's local laboratory, peripheral blood and bone marrow aspirate/biopsy with flow cytometry assessment(s) MRD analysis should be done for CLL patients with evidence of CR in all of the response parameters (ie, hematology, CT scan). The marrow samples may be aligned with the bone marrow aspirate and biopsy sample used to confirm CR. If not available at a site's local laboratory, these samples are considered optional.

7.8. Safety Follow-up

Approximately 28 days after the last administration of the study drug, all patients should return for a final evaluation. Assessments to be performed are presented in Appendix 7, Table 5.

Any abnormal finding of clinical consequence and not related to the disease progression will be monitored until resolution or baseline status.

7.9. Long-Term Follow-Up

Patients who discontinue study drug due to reasons other than disease progression will remain on study and should be followed every 3 months until patient exhibits first progression, starts new anticancer therapy, death, or study closure, whichever occurs first.

Patients may withdraw from long-term follow-up and still remain on study in Survival Follow-up with approval of the medical monitor.

7.9.1. Survival Follow-up

Patients that discontinue study drug and have progressed (or chosen to withdraw from long-term follow-up) will enter into survival follow-up. During survival follow-up, patients will not return to the clinic but will be contacted every 3 months by telephone to assess survival until death or end of study (Section 4.3.1.2), whichever occurs first.

8. QUALITY CONTROL AND QUALITY ASSURANCE

According to the GCP guidelines the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s).
- Certified local laboratories for laboratory measurements and ECGs.
- Study center initiation visit.
- Early study center visits post-enrollment.
- Routine study center monitoring.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, the sponsor and/or the clinical research organization (CRO) clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, central laboratories, vendors, clinical database, and the final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

8.1. Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor and/or CRO monitors will contact the study center prior to the patient enrollment to review the protocol and data collection procedures with the study center personnel. In addition, the Monitor will periodically contact the study center, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the Monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol (and any versions), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.5.

8.2. Data Management/Coding

Data required by the protocol will be entered into the eCRFs in an electronic data capture (EDC) system that is compliant with all regulatory requirements.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines (eCCGs). 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 FDA 1572 must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

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

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

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

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

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA® Version 18.1 or higher.

8.3. Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

9. SAFETY MONITORING AND REPORTING

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

9.1. Adverse Events

9.1.1. Definition and Reporting of an Adverse Event

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

Examples of an AE include:

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

Examples of an AE do not include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The

investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.1.1.1. Assessment of Severity (Intensity)

The investigator will make an assessment of severity (intensity) for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI CTCAE v4.03.

Toxicities that are not specified in the NCI-CTCAE will 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 (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade1], 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 9.2.

9.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

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

The causality of each AE should be assessed and classified by the investigator as “related” or “not related”. An AE is considered related if there is “a reasonable possibility” that the AE may have been

caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

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

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

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

9.1.1.3. Follow-up of Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. Once resolved, the appropriate AE or SAE page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be resent to the sponsor within the time frames outlined in Section 9.4.1.

9.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation) or other abnormal assessments (ECGs, X-rays, vital signs) that are judged by the investigator as clinically significant will be recorded as 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worse will not be reported as adverse events or serious adverse events. The definition of clinically significant is left to the judgment of the investigator; in general these are events that result in clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation

The investigator will exercise his/her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.2. Definition of a Serious Adverse Event

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

- Results in death.
- Is life-threatening.

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an 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 has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

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

- 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 with or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

9.3.1. Adverse Event Reporting Period

After informed consent has been signed, but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 28 days after the last study treatment of zanubrutinib. After this period, the investigator should report any SAEs or AEs that are believed to be related to prior study drug treatment.

9.3.2. Eliciting Adverse Events

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

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

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

9.3.3.1. Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

9.3.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (eg, clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report, if applicable). However, if a patient initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

9.3.3.3. Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, it should be recorded as a new AE on the eCRF (and a stop date should be recorded in the previous AE).

A recurrent AE is one that occurs and resolved between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

9.3.4. Disease Progression

Disease progression is expected in this study population, and the term "disease progression" should not be reported as an AE term. When disease progression is identified, the AE that identifies the disease progression should be reported as the AE term. For instance, a patient with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as "pleural effusion" instead of disease progression or metastasis to lungs. If a patient has a seizure that is determined to be associated with a brain metastasis, the term "seizure" should be recorded as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data. They should not be reported as an SAE. A patient death not solely due to disease progression as assessed by the investigator should be reported as an SAE immediately, regardless of relationship to study drug.

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

9.3.4.1. Death

When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death."

9.4. Prompt Reporting of Serious Adverse Events

9.4.1. Time Frames for Submitting Serious Adverse Events

Serious adverse events will be reported promptly to the sponsor or designee as described in Table 4 once the investigator determines that the event meets the protocol definition of an SAE.

Table 4 Time Frame for Reporting Serious Adverse Events

	Time frame for making Initial Report	Documentation method	Time frame for making follow-up report	Documentation	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE Report Form	As expeditiously as possible	SAE Report Form	Email or fax SAE form or pregnancy form

Abbreviations: SAE, serious adverse event

9.4.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.4.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE signed by the investigator and forwarded to the sponsor within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the SAE and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.1.2.

The sponsor will provide contact information for SAE receipt.

9.4.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.3.3. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate projects contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

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

This protocol is being filed under an Investigational New Drug (IND) protocol amendment with the United States FDA. Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators files to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

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

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.5. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving zanubrutinib or within 90 days of 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 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

9.6. Post-study Adverse Event

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, defined in Section 9.3.1.

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

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

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- BGB-3111 Investigator's Brochure

10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1. Sample Size Considerations

The number of dose levels examined and the emerging zanubrutinib toxicities will determine the sample size. It is anticipated that approximately 25 patients in Part 1 will be required to establish the selected dose and schedule of zanubrutinib when administered as a single agent and approximately 380 patients will be required to further evaluate efficacy and safety of zanubrutinib in the separate disease cohorts in Part 2.

10.2. Efficacy Analyses

Efficacy is not a primary objective of the study. Efficacy assessments will use the applicable criteria to assess overall disease response (see Section 7.3, Appendix 3). For analysis based on independent review results, IgM-only response will also be used for WM and CT-based response will also be used for MCL. Efficacy data in Parts 1 and 2 will be summarized separately. Within Part 2, efficacy endpoints will be summarized by disease cohort.

PFS is defined as the time from the first dose of zanubrutinib to date of disease progression or death. OS is defined as the time from the first dose of zanubrutinib to date of death due to any reason. DOR is defined as the date the response was first recorded to the date on which progressive disease is first noted or the date of death due to any cause. Kaplan-Meier methodology will be used to estimate PFS, OS and DOR medians, and their 95% CI will be constructed using Brookmeyer and Crowley method. Kaplan-Meier curves will be provided for PFS, OS, and DOR.

Overall response rate (ORR), complete response rate (CRR), and MRD clearance rate will be determined in the safety analysis set along with 95% CI using Clopper-Pearson method.

Source imaging relevant to efficacy analyses (CT, PET/CT, etc.) may be requested by the sponsor as needed.

More details will be given in the statistical analysis plan.

10.3. General Considerations for Data Analysis

Refer to the statistical analysis plan for more details about how data will be listed and summarized.

10.3.1. Analysis Sets

All patients who are exposed to (or started receiving) zanubrutinib will be included in the safety analysis set. It will be the primary analysis population of efficacy and safety parameters. All patients for whom valid zanubrutinib PK parameters can be estimated will be included in the PK analysis set.

10.3.2. Interim Analysis

No formal interim analysis is planned for this study. Since this is a non-randomized Dose Escalation/Expansion study, the safety, efficacy, PK and pharmacodynamic data will be evaluated on an ongoing basis.

10.4. Safety Analyses

All summaries of the safety data will be provided for the safety analysis set. Safety data in Part 1 will be summarized separately by dose cohort. Within Part 2, safety data will be summarized by disease cohort. Safety data will also be summarized for the pooled dose levels from Parts 1 and 2 (based on total daily dose) and for the entire study population.

AEs and toxicities in laboratory data will be graded according to NCI-CTCAE, Version 4.03 or higher. AEs will be coded using the MedDRA Version 18.1 or higher.

SAE, treatment related AEs and AE leading to drug discontinuation will be summarized.

Hematology, clinical chemistry, coagulation, and urinalysis values and change from baseline values will be summarized. Summaries of toxicity grade at baseline versus the maximum toxicity grade will be provided.

10.4.1. Extent of Exposure

The number of cycles/days on treatment, total dose, of study treatment received, and the number of patients requiring dose modification and drug discontinuation due to AEs will be summarized.

10.4.2. Electrocardiogram

All ECG parameters including the QT interval corrected for heart rate (QTc) will be summarized at each assessment time. Change from baseline will also be summarized. Relationship between dose level and QTc changes will be explored by graphs. QTc will be calculated using both Fridericia's and Bazett's formulae.

10.5. Pharmacokinetic Analyses

Pharmacokinetic parameters will be derived using standard non-compartmental methods with WinNonlin Professional Version 5.2 or higher (Pharsight Corp., Mountain View, California) or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations.

Where possible, the following plasma PK parameters will be determined for BGB-311:

AUC	Area under the plasma concentration-time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method
AUC_{last}	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
$AUC_{0\text{-}24h}$ and AUC_{ss}	Area under the plasma concentration-time curve over the dosing interval from zero to 24h postdose
C_{max} and $C_{max,ss}$	Maximum plasma concentration
t_{max} and $t_{max,ss}$	Time of maximum plasma concentration
λ_z	Terminal rate constant
$t_{1/2}$	Terminal half-life
CL/F	Apparent systemic plasma clearance
V_z/F	Apparent volume of distribution during the terminal phase
RAUC	AUC accumulation ratio (AUC_{ss} Week 2 Day 1/$AUC_{0\text{-}24h}$ Week 1 Day 1)
RC_{max}	C_{max} accumulation ratio (C_{max} Week 2 Day 1/C_{max} Week 1 Day 1)

Summaries of the PK parameters will be provided.

Where possible, the following diagnostic parameters of the plasma PK analysis will be calculated and listed, but not summarized:

Interval	The time interval (hours) of the log-linear regression used to determine λ_z
n	Number of data points included in the log-linear regression analysis to determine λ_z (a minimum of 3 points will be used)
Rsq	Rsquare; coefficient of determination for calculation of λ_z. If Rsq is less than 0.800, then λ_z and related parameters will not be reported
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation; if greater than 20% then AUC and related parameters will not be reported

Additional PK parameters may be calculated if deemed appropriate.

Plasma zanubrutinib concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard non-compartmental and/or compartmental PK methods. The PK parameters for a single dose profile (AUC_{last}, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F) and after steady-state ($AUC_{last,ss}$, $C_{max,ss}$, $t_{max,ss}$), will be calculated, if there are sufficient data. Individual patient parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters) by dose level and schedule will be reported. Individual patient parameter values will be plotted against dose.

Dose proportionality of AUC, AUC_{ss}, C_{max}, and $C_{max,ss}$ for zanubrutinib will be assessed using the power model as described below and evaluated visually in graphical form:

A linear regression model with the logarithm of the PK parameter (AUC, C_{max}, AUC_{last}, AUC_{ss}, and $C_{max,ss}$) as the dependent variable and the logarithm of the dose as the independent variable ($\log[PK]=\alpha+\beta*\log[Dose]$) will be fitted. The model parameters (slope [β] and intercept [α]) will be estimated using least squares regression. A minimum of 3 values per dose must be available for a given PK parameter to estimate dose proportionality with the power model. Point estimates and corresponding 2-sided 95% confidence intervals for the slope parameter and the intercept parameter will be provided.

10.6. Pharmacodynamic Analyses

Pharmacodynamics is not a primary objective of this study. BTK occupancy in PBMCs and LN will be determined as scheduled in Table 6. Summaries of the data will be provided, if applicable.

10.7. Other Explorative Endpoints

[redacted]

11. STUDY COMMITTEES AND COMMUNICATION

11.1. Safety Monitoring Committee

The SMC consists of investigators, the sponsor's medical delegate, safety delegate, and the contract research organization's medical monitor. A separate charter will outline the details for the composition and responsibility of the SMC. Ad hoc members will be consulted as needed and may include, but are not restricted, to the biostatistician and pharmacokineticist. The SMC will be established for:

- Dose Escalation (Part 1): the determination of dose levels to be administered and dose regimen during dose escalation and will utilize the data available from the previous dose levels.
- Dose Expansion (Part 2): review of safety signals in a given cohort whereby ≥ 33% of at least 6 patients experience a DLT-like event (an event that would have met the criteria for a DLT if it had occurred during Dose Escalation).

12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1. 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 before the study is initiated at a study center in that country.

12.2. Investigator Responsibilities

12.2.1. Good Clinical Practice

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

12.2.2. 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.

12.2.3. Investigator Reporting Requirements

As indicated in Section 9.1, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

12.2.4. Confidentiality

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

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

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

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the ICF process, either as part of the ICF, or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location. Only patient initials (where allowed), date of independent central review, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

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

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

12.2.5. Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. This also applies to records for those patients who discontinue the study early. If a patient withdraws from the study, the reason must be noted in the appropriate eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRFs exist within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing an electronic signature within the EDC system. After final database lock, the Investigator will receive a copy of the patient data on CD-ROMs for archiving the data at the study site.

12.2.6. 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. Dispensation records will document quantities received from BeiGene, quantities dispensed to patients and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

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

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

12.2.7. Inspections, Audits, and Monitoring Visits

The investigator must ensure the facilities used and all the source documents for this trial should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

12.2.8. Protocol Adherence

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

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

12.3. Protocol Modifications

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

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

12.4. Study Report and Publications

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

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

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

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

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

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission 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 details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented 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 Sponsor to allow for patent filings in advance of the publication/presentation.

12.5. 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.
- Data queries.

- Accountability, reconciliation, and arrangements for unused investigational product(s).
- Review of study records for completeness.
- Return of treatment codes to the sponsor.
- Shipment of PK and pharmacodynamic samples to assay laboratories.

In addition, the sponsor reserves the right to temporarily 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 non-compliance with this protocol, GCP, the clinical study agreement or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused investigational product(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.

12.6. Records Retention and Study Files

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

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

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

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with

assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

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

Biological samples remaining after this study may be retained in storage by the sponsor for a period up to 2 years.

12.7. 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) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights, whether patentable or not, which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

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

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

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.

- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.
- Information which is necessary to disclose in order to provide appropriate medical care to a patient.
- Study results which may be published as described in Section 12.4.

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

12.8. Joint Investigator/Sponsor Responsibilities

12.8.1. Access to Information for Monitoring

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

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

12.8.2. Access to Information for Auditing or Inspection

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

13. REFERENCES

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14. APPENDICES

Appendix 1. Signature of Investigator

PROTOCOL TITLE: A Phase I, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies

PROTOCOL NO: BGB-3111-AU-003

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

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to PAREXEL International (IRL), Limited.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Appendix 2. Clinical Laboratory Assessments

Clinical Chemistry	Hematology	Coagulation	Urinalysis	Immunoglobulin Assessment and Serum EPG
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Bicarbonate Calcium Chloride Creatinine Glucose Lactate dehydrogenase Magnesium Phosphorus Total protein Potassium Sodium Total and direct bilirubin[3] Urea Uric Acid	Hemoglobin Reticulocyte count Platelet counts WBC count with differential Neutrophil count Bands (optional) Lymphocyte count Eosinophil count	Prothrombin time Partial thromboplastin time International normalized ratio	pH Specific gravity Glucose Protein Blood Ketones 24 hour protein[1] Random urine protein to creatinine ratio[1]	IgA IgG IgM Serum EPG[2]

1. On routine urinalysis, if urine protein is ≥ 2+ by dipstick and clinically significant, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.
2. Serum EPG on 1st test for all WM patients, and if a paraprotein is present, repeated on all subsequent immunoglobulin assessments.
3. When the level of total bilirubin is normal, direct bilirubin measurement is not required.

Appendix 3. Response Criteria

Appendix 3A. Response Definition after Treatment for Patients with CLL (Hallek 2008 and Cheson 2012)

Parameter	CR*	PR*	PR-L:	PD*	SD*
Group A					
Lymphadenopathy‡	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion	Absence of response or PD
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%	Absence of response or PD
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%	Absence of response or PD
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	**	Absence of response or PD
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules		Absence of response or PD
Group B					
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Absence of response or PD
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL	Absence of response or PD
Neutrophils‡	> 1500/µL	> 1,500/µL or > 50% improvement over baseline	> 1,500/µL or > 50% improvement over baseline		Absence of response or PD

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

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

CR*: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR*: at least two of the criteria of group A (lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes) plus one of the criteria of Group B (platelets, hemoglobin, or neutrophils) have to be met (with the exception of patients who have only one abnormal group A criteria at baseline, who have to meet one of the criteria of group A plus one of the criteria of Group B); 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 neutrophils have to be met; SD*: is absence of progressive disease (PD) and failure to achieve at least a PR; PD*: at least one of the above PD criteria has to be met.

** Note: In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD (Cheson, 2012).

† Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination)

‡ These parameters are irrelevant for some response categories

Appendix 3B. Modified Lugano Classification for Non-Hodgkin Lymphoma (Cheson, 2014)

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 (e.g., 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 If bone marrow was negative at baseline, bone marrow confirmation at post-baseline is not required.
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 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 Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Target nodes/nodal masses, extranodal lesions		
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**	Progressive metabolic disease	Progressive disease requires at least 1 of the following cross product of the longest transverse diameter of a lesion and perpendicular diameter progression:
Individual target nodes/nodal masses	Score 4 or 5† with an increase in intensity of uptake from nadir and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: • longest transverse diameter of a lesion > 1.5 cm and • Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and • An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., 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
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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

Abbreviations: CT: computed tomography; FDG: [18F] fluorodeoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography.
Modified from Cheson, 2014.
*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials 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 six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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

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

**Progressive disease must be confirmed by repeat imaging no sooner than 4 weeks from the first imaging that show possible progression to rule out pseudo-progression (For additional details, refer to Section 7.3.1 Computed Tomography). Patients may continue study treatment while they wait for the confirmation imaging.

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/disease flare" should be selected for such instances. Following the repeat imaging 10 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

Appendix 3C. Categorical Waldenström's Macroglobulinemia Response Definitions (Modified Owen 2013)

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)[a, d]
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline (or normal serum IgM level) [a] Improvement in extramedullary disease, lymphadenopathy/splenomegaly if present at baseline [a, d] 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) [a, d]
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) [c]	At least one of the following: • Confirmed ≥25% increase in serum IgM and total increase of ≥500 mg/dL from nadir (on treatment)[b, c] • New lymph nodes >1.5 cm, or ≥50% increase from nadir in 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

[a] For response assessments that occur during cycles where a CT scan is not required then results from prior scans (up to 12 weeks during the first 48 weeks and up to 24 weeks thereafter) can be carried forward in those patients with extramedullary disease at baseline

[b] Sequential changes (separated by at least 4 weeks) in IgM levels should be determined by the IgM value from the quantitative serum immunoglobulin assay, unless for assay limitations this is not possible, in which case the M protein/ paraprotein level by densitometry (SPEP/EPG) will be used

[c] Isolated increase in serum IgM levels during periods of study drug withholding will not be considered as progressive disease unless confirmed by a repeat serum IgM level at least 6 weeks after restarting study drug administration and accompanied by a total increase of at least 25% and ≥ 500 mg/dL from lowest nadir. Please see Guidelines for specific clinical or laboratory circumstances below.

[d] If only physical exam (PE) is available and the clinical assessment is indicative of an unequivocal improvement from baseline (ie, enlarged spleen has regressed, abnormal lymph nodes have reduction in measurements), then the reduction in extramedullary disease can be assessed by PE alone.

Guidelines for specific clinical or laboratory circumstances:

1. *Baseline serum total IgM value above the laboratory limit of quantitation.*

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

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

   If the baseline 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.

3. *Patients with documented cryoglobulinemia.*

   For patients with abnormal cryoglobulin results, serum quantitative immunoglobulins and serum electrophoresis protein globulins (EPG), as well as immunofixation and cryoglobulin as applicable, should be tested using samples collected and processed under warm conditions. Sequential response assessments for individual subjects should be performed using results based on the same methodology, and either IgM or paraprotein.

4. *Plasmapheresis*

   Patients may undergo plasmapheresis, when clinically indicated, during the first two cycles of study treatment. A pre-plasmapheresis serum total IgM and M-protein must be obtained during the screening period or the highest pre-dose value will serve as the baseline value for response assessment throughout the study. IgM response and nadir determination should be at least 4 weeks following the last plasmapheresis procedure. Patients requiring plasmapheresis after cycle 2 will be adjudged to have progressive disease.

5. *Assigning Response in the Case of Drug Hold*

   Isolated increase in serum IgM levels during periods of study drug withholding will not be considered as progressive disease unless confirmed by a repeat serum IgM level at least 6 weeks after restarting study drug administration and accompanied by a total increase of at least 25% and 500 mg/dL from lowest nadir. The response category “IgM flare/disease flare” should be selected for such instances. Following the repeat serum IgM level 6 weeks after restarting study drug, response should be in comparison to the serum IgM level at baseline.

   Similarly, isolated increase in extramedullary disease, lymphadenopathy or splenomegaly during periods of study drug withholding 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 "disease flare" should be selected for such instances. Following the repeat imaging 10 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

6. *Missing CT Scans*

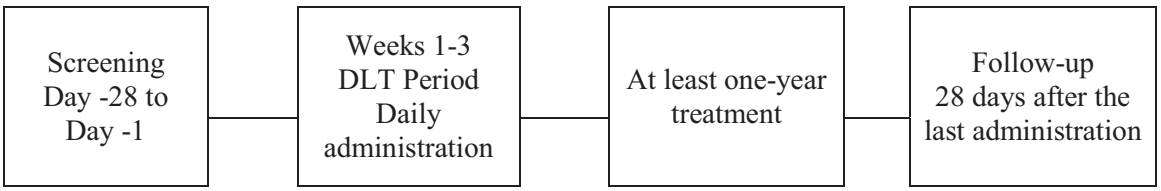
If a required CT scan timepoint is missed, it should be performed as soon as possible. In cases where a single CT scan timepoint is missed and the subsequent CT scan findings remain the same or improved from the prior scan, response can be assessed for the intervening cycles using the CT scan obtained prior to the missed CT scan. If 2 consecutive CT scan timepoints are missed, then the best response that can be assessed during those cycles is an MR (minor response).

Appendix 3D. Hairy Cell Leukemia (HCL) Response Criteria (Grever 2017)

Complete Response (CR)	Near normalization of peripheral blood counts: hemoglobin >11 g/dL (without transfusion); platelets >100 000/mL; absolute neutrophil count >1500/mL. Regression of splenomegaly on physical examination. Absence of morphologic evidence of HCL on both the peripheral blood smear and the bone marrow examination.
Partial Response (PR)	Near normalization of the peripheral blood count (as in CR) with a minimum of 50% improvement in organomegaly and bone marrow biopsy infiltration with HCL.
Stable Disease (SD)	Patients who have not met the criteria for an objective remission after therapy are considered to have SD.
Progressive Disease (PD)	Increase in symptoms related to disease, a 25% increase in organomegaly, or a 25% decline in their hematologic parameters

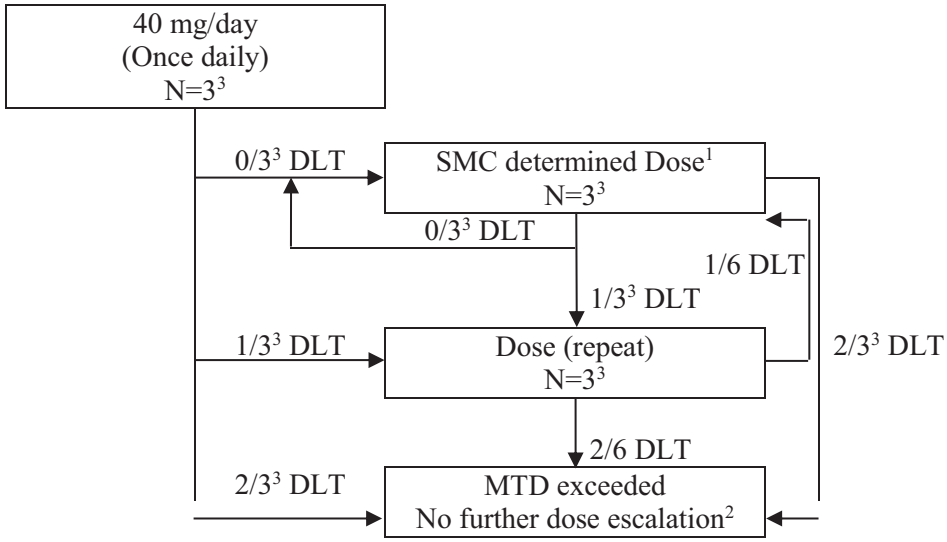
Appendix 4. Flow Chart

Overall Study Design



Refer to Table 1 for Suggested Dose Escalation Scheme.

Dose Escalation



1. If 0 of the patients in the cohort experience a DLT by the end of Cycle 1, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the Safety Monitoring Committee (SMC). If a DLT occurs in 1 of the patients, additional patients will be treated at that dose level, up to a maximum of 6 patients in total. If 1 out of 6 patients experience a DLT during DLT assessment period, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the SMC.
2. No additional patients will be treated at a given dose level if 2 or more out of 3 or 6 patients develop a DLT during DLT assessment period. In this instance, the MTD is considered to have been exceeded.
3. Additional patient(s), up to a maximum of 6 patients in total, will be enrolled if more than 3 patients have been screened and are eligible for the cohort. The DLT assessment and dose-escalation scheme will follow the same principle as stipulated for the standard 3+3 design. For example, 3 additional patients will be enrolled if a DLT is observed in 1 of 3 patients; 2 additional patients will be enrolled if a DLT is observed in 1 of 4 patients; and 1 additional patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1 of 6 patients.
4. If the MTD is exceeded, the next lower dose level is planned to be taken forward into Expansion part. Depending on the decision of the SMC and on review of available data, an additional intermediate dose level, between the MTD exceeding dose level and the next lower dose level, may be explored prior to a final decision on the Expansion dose.
5. In the event that a MTD is not identified due to paucity of DLTs, the Expansion schedule will be based on PK, pharmacodynamic studies of BTK inhibition in PBMCs, safety, tolerability, and preliminary efficacy.

Appendix 5. CYP3A Inhibitors and CYP3A Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
CYP3A4, CYP3A5, CYP3A7
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice)
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Abbreviation: CYP: cytochrome P450.

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

Source: Food and Drug Administration Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

Appendix 6. CYP2C8, CYP2C9, and CYP2C19 Substrates

CYP2C8 Substrates	CYP2C9 Substrates	CYP2C19 Substrates
repaglinide[1]	celecoxib	**Anti-epileptics:**
Paclitaxel	phenytoin[2]	S-mephenytoin[1,2]
	warfarin[2]	
		Proton-Pump Inhibitors
		lansoprazole[1]
		omeprazole[1]

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

1. Sensitive substrates: Drugs that exhibit an area under the plasma concentration time curve (AUC) ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.
2. Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

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

Source: Food and Drug Administration Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

Appendix 7. Study Assessments and Procedures Schedule

Table 5 Study Assessments and Procedures Schedule for Part 1 and Part 2

	Screening [1]	Treatment Period [2]					Safety Follow-up [3]	Long-term Follow-up [4]	Survival Follow-up [5]
		Weeks 1 to 4 (DLT period is W1 to 3)		Weeks 5 to 8	Weeks 9 to 52	Weeks 53+			
Days	-28 to -1	W1D1	W2D1	W5D1	Every 4 weeks	Every 12 weeks	28 days after last dose	Every 3 months	Every 3 months
Window (days) [6]		± 0	± 1	± 3	± 3	± 10	± 7	± 7	± 7
Informed consent [7]	X								
Review inclusion/exclusion criteria	X								
Demographic data	X								
General medical history & baseline conditions	X								
Vital signs	X	X	X	X	X	X	X	X	
Weight (& Height at screening)	X	X		X	X	X	X	X	
B symptoms [8]	X	X		X	X	X	X	X	
Complete physical examination [9]	X								
Targeted physical examination [9]		X	X	X	X	X	X	X	
ECOG performance status	X	X		X	X	X	X		
Echocardiogram	X								
12-lead ECG [10]	X	X	X	X	As clinically indicated		X [10]		
Review of patient diary		X	X	X	X	X			
Review of concomitant medications	X	X	X	X	X	X	X		
Adverse events (including serious)		X	X	X	X	X	X		
CT scan [11]	X	Year 1: Every 12 weeks (end of Weeks 12, 24, 36 and 48) Year 2: Every 24 weeks beginning Week 76; for MCL patients: Every 12 weeks beginning Week 64[12]					X	X [12]	
Whole body FDG-PET scan or an integrated PET/CT scan [11]	X	At time of CR (if PET positive at screening)							
Bone marrow biopsy and aspiration [13]	X	End of Week 12 and at time of CR/RT				At time of CR/RT			
Response Assessment [14]		Every 12 weeks (end of Weeks 12, 24, 36 and 48)				X [12]	X[11, 14]	X	
Study drug administration [15]		X							

	Screening [1]	Treatment Period [2]					Safety Follow-up [3]	Long-term Follow-up [4]	Survival Follow-up [5]
		Weeks 1 to 4 (DLT period is W1 to 3)		Weeks 5 to 8	Weeks 9 to 52	Weeks 53+			
Days	-28 to -1	W1D1	W2D1	W5D1	Every 4 weeks	Every 12 weeks	28 days after last dose	Every 3 months	Every 3 months
Window (days) [6]		± 0	± 1	± 3	± 3	± 10	± 7	± 7	± 7
Survival Follow-up									X [5]
LOCAL LABORATORY STUDIES									
Hematology [16]	X	X	X	X	X	X	X	X	
Clinical chemistry [17]	X	X	X	X	X	X	X	X	
Coagulation	X	X		X	X	X	X		
IgA, IgG, IgM level and serum EPG [18]	X			X	X	X	X	X	
β2-microglobulin [18]	X								
Pregnancy test [19]	X	X		X	X	X			
Viral serologies [20]	X								
Urinalysis [21]	X	X	X	X	X [21]	X [21]	X		
CLL prognostic factors blood sample [22]	X								
MRD blood sample [23]		At the time of CR							
MRD tissue sample [23]									
CENTRAL LABORATORY STUDIES									
Correlative blood sample [24]	X			X	X				
Pharmacokinetic blood sampling		Refer to Table 6 for Part 1 and Table 7 for Part 2 Refer to Table 8 for patient participating in drug product PK profiling							
Pharmacodynamic blood sampling									
Pharmacodynamic (tissue) sampling [25]	X								
Tumor tissue sampling [26 & 27]	X	At time of disease relapse							
Blood or bone marrow sample collection for resistance analysis [27]									

Abbreviations: CLL: chronic lymphocytic leukemia; CT: computed tomography; CR: complete response; D: day; DLT: dose limiting toxicity; ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; EPG: electrophoresis protein globulins; FDG: fluorodeoxyglucose; Ig: immunoglobulin; MRD: minimal residual disease; PET: positron emission tomography; RT : Richter's transformation; W: week; X: to be performed

Assessments scheduled on study drug administration days should be performed prior to dosing, unless otherwise specified.

1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. Screening assessments completed within 72 hours of administration can be used as Day 1 assessments.
2. The duration of treatment will be until any of the events listed in Section 4.3.

3. The Safety Follow-up Visit will occur within 28 days after the last dose of zanubrutinib (± 7 days).
4. Patients who discontinue study drug due to reasons other than disease progression will remain on study and should be followed every 3 months until patient exhibits first progression, starts new anticancer therapy, death or study closure, whichever occurs first (see Section 5.5.6). Patients may withdraw from long-term follow-up and still remain on study in Survival Follow-up with approval of the medical monitor.
5. Patients that discontinue study drug and have progressed (or chosen to withdraw from long-term follow-up) will enter into survival follow-up. During survival follow-up, patients will not return to the clinic but will be contacted every 3 months by telephone to assess survival until death or end of study, whichever occurs first (see Section 7.9.1).
6. Windows: days allowed for reschedule of an entire visit due to logistic reasons (eg, public holidays). In all cases, including on W1D1, elements relating to medical assessment may be performed 24 hours prior to the scheduled day. These are: B symptoms, physical examination, ECOG, concomitant medications, adverse events (AE), hematology, clinical chemistry, coagulation, pregnancy test, and urinalysis.
7. Written informed consent form(s) must be signed by the patient before any study-specific procedures are performed.
8. Unexplained weight loss > 10% over previous 6 months, fever (> 38°C), and/or drenching night sweats.
9. Complete physical exam includes all systems described in the body of the protocol. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms.
10. Perform a single 12-lead electrocardiogram (ECG) in triplicate at Screening and at the treatment completion/early termination visit. Beginning at Week 9, this test will be performed as clinically indicated. ECG time points for pharmacokinetic (PK) sampling will be obtained as per Table 6. Note: not all required ECGs are indicated in the above table (Table 5). Further details can be found in Section 7.2.2.
11. Positron emission tomography (PET) or integrated PET at screening is at the investigator's discretion. Computed tomography (CT) scan with contrast tumor assessments must be performed within 7 days of the specified time points and at disease progression. CT scans must encompass neck, chest, abdomen and pelvis, and include oral and intravenous contrast. A CT scan of diagnostic quality performed as part of PET/CT is acceptable, provided that bidimensional nodal and liver/spleen measurements can be made. Magnetic resonance imaging (MRI) may be used in place of CT in clinical scenarios where anatomical location of an evaluable lesion (such as soft tissue) precludes accurate measurement by CT. If the patient has no assessable disease by CT at study entry (eg, Waldenström's macroglobulinemia [WM] without nodal enlargement), repeat scans are not required. The CT scan will be used for disease assessment by the investigator at each study center. For scheduled scans, if a scan has been done within 4 weeks of the scheduled time, it does not need to be repeated. For patients who discontinue early, a CT scan will be performed at the discontinuation visit if the previous scan was more than 3 months prior. Patients with confirmed CR may choose to either have scans performed every 24 weeks or as specified in the schedule, whichever is less frequent. The Week 48 scan is always required, regardless of patient status. For time points where imaging is not required, a physical exam may be used in its place. The frequency of CT scans for patients with hairy cell leukemia could follow institutional standards after Week 52.
12. Appropriate imaging for response assessment should be conducted every 12 weeks starting from Week 64 (end of Weeks 64, 76, 88, 100), and every 24 weeks thereafter after Week 100 or when a significant change in response is suspected (Progressive Disease [PD] or upgrade of response). For patients with MCL, after Week 52, appropriate imaging for response assessment should be conducted every 12 weeks starting from Week 64 (end of Weeks 64, 76, 88, 100) and every 24 weeks thereafter from Week 100 or when a significant change in response is suspected (PD or upgrade of response).
13. A bone marrow examination must be performed at Screening for all patients, and within 7 days of the end of Week 12 for patients with baseline marrow involvement. Thereafter, bone marrow examination is only required for patients with baseline marrow involvement who need bone marrow examination to confirm CR. For WM patients, suspected progression due to disease transformation should be confirmed by a bone marrow / biopsy examination, e.g. Richter's transformation (RT). (see Section 7.3.3). Patients who are otherwise complete responders, but are positive for bone marrow involvement, should recheck bone marrow as clinically indicated, but at a minimum of at least once per year until CR is confirmed.

14. Response should be assessed against baseline per disease relevant instructions in Appendix 3. Physical exam should be used at any time points where imaging is not required, but physical exam revealing disease progression or potential progression may require confirmation via imaging. Visits that contain components sufficient to determine a change in overall response in the patient (i.e. unscheduled CT scans and labs, IgM-based change response between scheduled efficacy assessments for WM patients) should complete an overall efficacy response assessment as needed.
15. The study drug will be taken once (QD) or twice a day (BID). For the BID cohort, patients will take repeated drug administration twice daily (once in the morning and once in the evening with 12 ± 2 hours apart), starting from Day 1 (refer to Section 5.3 for detailed instruction).
16. Hematology, including hemoglobin, reticulocyte count, white blood cell (WBC) count, absolute differential count (neutrophils, eosinophils, lymphocytes,) and platelet count. In the event of neutropenia (absolute neutrophil count < 1000/mm^3) or thrombocytopenia (platelets of less than 50,000/mm^3), these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.
17. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.
18. Serum electrophoresis protein globulins (EPG) on 1st test for all WM patients, and if a paraprotein is present, repeated on all subsequent immunoglobulin assessments. For all WM patients, a β2-microglobulin value within 90 days of W1D1 will be collected**,** and if cryoglobulin is present at baseline, repeat cryoglobulin assessments as clinically indicated and to confirm CR. For patients with abnormal cryoglobulin result, serum quantitative immunoglobulins and serum electrophoresis protein globulins (EPG) should be tested using samples collected and processed under warm conditions. Immunofixation will be performed as clinically indicated to confirm CR.
19. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at Screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
20. Viral serologies include: hepatitis B (HBsAg, total HB core antibody [anti-HBc] and HBsAb as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status); hepatitis C virus (HCV) antibody (as well as HCV RNA by PCR if the patient is HCV antibody positive). Patients who are HBsAg-negative, HBcAb-positive and HBV DNA-negative must undergo monthly HBV DNA screening by PCR. Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.
21. Collect urine dipstick, as well as urine microscopy if dipstick is abnormal. If urine protein is ≥ 2+ by dipstick and clinically significant, a 24-hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated (see Section 7.4). After Week 9, this test will be performed as clinically indicated.
22. Patients with CLL should have a blood sample sent at screening for cytogenetic analysis, including: immunoglobulin variable region heavy chain (IgHV) mutational status and interphase fluorescent in situ hybridization (FISH) for chromosomal abnormalities including 17p-, 11q-, 13q- and +12.
23. For CLL patients with evidence of CR in all of the response parameters (ie, hematology, CT scan), peripheral blood and bone marrow aspirate/biopsy with flow cytometry assessment(s) MRD analysis should be done if available at a site's local laboratory.
24. Correlative blood will be collected for platelet functional assay (citrate blood) and host immunity analysis (acid citrate dextrose [ACD] blood). ACD blood will be collected for all patients in Part 1. In Part 2 of the study, ACD blood will only be collected for approximately 7 CLL patients at sites located in Melbourne. Collect 30 ml ACD blood on the date indicated, transport within 8 hours to the central laboratory. For patients enrolled for Part 1, an additional 30 ml of citrated blood will be collected at Screening, and on Week 5 Day 1, transported within 3 hours to the central laboratory.
25. Expansion (Part 2) only. This is mandatory for Cohort 2a and optional for Cohorts 2b to 2j. Two lymph node needle cores are collected at Screening, and repeated on W1D3, within 2 hours prior to zanubrutinib administration on that day. These specimens are used to determine BTK occupancy in tissue sites. The pharmacodynamic tissue sampling will be stopped when Version 6 is active.

26. Patients to be enrolled in Cohort 2b must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype [redacted]. Patients to be enrolled in Cohort 2l must have histologic confirmation of Richter's transformation prior to enrollment. Patients enrolled to all other cohorts should have archival tumor tissues available or agree to a tumor biopsy [redacted].
27. Patients who have disease relapse at any time will be asked for blood samples, a bone marrow aspirate/ biopsy sample or to undergo re-biopsies of representative tumor sites to obtain samples for studying mechanisms of resistance (see Section 7.7.3).

Table 6 Pharmacokinetic and Pharmacodynamic Sampling for Part 1

Procedure	**W1D1**							**W1 D2**	**W1 D3**	**W2D1**							**W5D1**	**W9D1**
Hours	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**8**	**24** [1]	**Pre-dose**	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**8**	**Pre-dose**	**Pre-dose**
ECG time points for pharmacokinetic (PK) sampling	X		X [3]	X [3]		X [3]	X [3]	X		X							X	X
Vital signs	X	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X	X	X	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X	X
PK blood sampling	X [4]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [4]	X [4]	X [4]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [4]	X [4]
Pharmacodynamic blood sampling	X [4]					X [2]		X [4]	X [4]	X [4]								

Abbreviations: ECG: electrocardiogram; D: day; PK: pharmacokinetic; W: week; X: to be performed

General note: It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK/pharmacodynamic sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) vital sign measurements; 3) PK/pharmacodynamic blood samples (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that time point.

1. On W1D2, before the morning dose.
2. A window period of ±20 minutes exists.
3. A window period of ±30 minutes exists.
4. Within 2 hours prior to dosing.

Note: Should a patient undergo an intra-patient dose escalation (refer to Section 4.1.1.2), additional blood PK samples will be taken to determine the plasma concentration of zanubrutinib. The samples should be taken on the closest visits after patients complete 4 weeks and 8 weeks of the new dose. These samples should be taken pre-dose on the required days. Additional PK samples may be taken if needed, to further evaluate zanubrutinib exposure. The investigator must record the time points for PK sampling and the time of dose administration before PK sampling in electronic Case Report Forms (eCRF).

Table 7 Pharmacokinetic Sampling for Part 2

Procedure	**W2D1**	
Hours	**Pre-dose**	**2**
Pharmacokinetic blood sampling	X[1]	X [2]

Abbreviations: ECG: electrocardiogram; D: day; W: week; X: to be performed

General note: It is important that pharmacokinetic sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the pharmacokinetic (PK) sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) PK blood samples (to be performed at the precise protocol scheduled time); and 3) any other scheduled or unscheduled measurements at that time point.

1. Within 2 hours prior to dosing.
2. A window period of ±20 minutes exists.

Note: Should a patient undergo an intra-patient dose escalation (refer to Section 4.1.1.2), additional blood PK samples will be taken to determine the plasma concentration of zanubrutinib. The samples should be taken on the closest visits after patients complete 4 weeks and 8 weeks of the new dose. These samples should be taken pre-dose on the required days. Should a drug-drug interaction (DDI) between zanubrutinib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction. Additional PK samples may be taken if needed, to further evaluate zanubrutinib exposure. The investigator must record the time points for PK sampling and the time of dose administration before PK sampling in eCRFs.

Table 8 Pharmacokinetic Sampling for New Drug Product Characterization*

Hours	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**8**
PK blood sampling	X [1]	X[2]	X [2]	X [2]	X[2]	X [2]	X [2]

*If at all possible, PK blood sample collection will occur on the first day when a new drug product (from a different manufacturing site) is used by patients.

Abbreviation: PK: pharmacokinetic; X: to be performed

1. Within 2 hours prior to dosing
2. A window period of ±20 minutes exists.

Appendix 8. Protocol Version History

Original Protocol, Version 1.0	22 April 2014
Protocol Version 2.0	31 August 2014
Protocol Version 3.0	02 December 2014
Protocol Version 4.0	24 June 2015
Protocol Version 5.0	11 January 2016
Protocol Version 6.0	09 September 2016
Protocol Version 6.1 (UK)	14 December 2016
Protocol Version 6.1 (South Korea)	07 March 2017
Protocol Version 6.2 (South Korea)	16 March 2017
Protocol Version 7.0	02 October 2017
Protocol Version 7.1 (South Korea)	05 March 2018