Clinical Study Protocol

Protocol Title:	A Phase 2 Study to Assess the Safety, Tolerability, and Activity of BGB-3111 in Combination with Rituximab in Chinese Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)
Protocol Number:	BGB-3111-213
Study Phase:	2
Investigational Product(s):	Zanubrutinib (BGB-3111)
Indication:	Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)
Sponsor:	BeiGene (Beijing) Co., Ltd No. 30 Science Park Road, Zhong-Guan-Cun Life Science Park Changping district, Beijing 102206
Sponsor Medical Monitor:	[redacted]
Version 1.0 (Original Protocol):	22 June 2017
Version 2.0 (Protocol Amendment 1.0):	28 March 2019

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PROTOCOL APPROVAL SHEET

PROTOCOL TITLE: A Phase 2 Study to Assess the Safety, Tolerability, and Activity of BGB-3111 in Combination with Rituximab in Chinese Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)

PROTOCOL NO: BGB-3111-213

DATE OF PROTOCOL: 28 March 2019

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[redacted] **Date**

Sponsor Medical Monitor

PROTOCOL AMENDMENT, VERSION 1.0, RATIONALE

The main purpose of this protocol amendment is as follows:

- To add the result of a drug-drug interaction study with the strong CYP3A inhibitor or inducer (BGB-3111-104) in text and tables with correlating content revised in number-updated Appendix 5;
- To add the result of a thorough QT study (BGB-3111-106) and remove QT/QTc interval prolonging medications and correlating contents in tables/appendixes;
- To add the result of a cocktail drug-drug interaction study (BGB-3111-108) and correlating concomitant medications content with Appendix 7 removed;
- To clarify and add urinalysis and optional urea test as a replacement of BUN in comprehensive serum chemistry panel for safety and tolerability assessment;
- To add supplementary pathology information and baseline information collected retrospectively (eg, EBV infected history and IPI score) for exploratory analysis;
- To use 5-point causality assessment scale for AE causality instead of 2-point causality assessment;
- To revise the text for clarity and consistency of the definition of safety follow-up and AE/SAE assessment period;
- To use the International Nonproprietary Name ‘zanubrutinib’ for BGB-3111;
- To revise the abbreviation in the list, text and under tables according to the Style Guide in BeiGene.

Throughout are administrative updates, editorial changes, and/or style and formatting revisions made with the purpose of improving clarity and consistency. Additionally, changes were made to the synopsis to match changes made in the protocol body.

Key changes made from the Version 1.0 (dated 22 June 2017) to Version 2.0 (19 March 2019), are summarized in the protocol sections below:

- In section 1.1.1, Summary of Relevant Non-clinical Data with zanubrutinib: revised the text of CYP according to the latest non-clinical data;
- Added section 1.1.5, Clinical Pharmacology: updated the information of QT interval prolongation and drug-drug interaction potential of zanubrutinib;
- In section 1.3, Study Rationale: corrected the referred study BGB-3111-1004 as BGB-3111-1002;
- In section 3.2, Secondary Endpoints: deleted 'nature' of AEs to clarify the safety and tolerability evaluation of zanubrutinib;
- In section 4, Study Design:
  - added 'disease progression or' to clarify the continuation period of Rituximab in consistence with the text in the protocol;
  - replaced Internal Monitoring Committee (IMC) with Safety Monitoring Committee (SMC) in performing the safety evaluation of the study and deleted the text of additional IMC meetings;
- In section 4.1, Duration of Study: revised the text to clarify the duration of study;
- In section 5.1, section 7.1.1, section 7.2.3 and the number-updated footnote 19 in Appendix 2: added 'to meet requirement of biomarker analysis' to specify the archival tumor tissue and/or a fresh tumor biopsy collected for screening;
- In section 5.1, Inclusion Criteria:
  - item 4: added 'occurring more than 6 months after the completion of last therapy' to specify the definition of relapsed disease;
  - Item 5 a: corrected the order of magnitude of numberings for previous formatting error;
- In section 5.2, Exclusion Criteria item 19 a: revised the wording to clarify the period of performing anti-viral therapy and monthly monitoring on eligible patients (also in Table 4);
- In section 6.2.1 and 6.2.2: deleted correlating text that may lead issues later;
- In section 6.2.1 and 6.2.3: modified the wording to clarify study treatment preparation and dispensation;
- In section 6.4.1, Zanubrutinib: revised the text to clarify the role of investigator in study drug administration;

- In section 6.5.2, BGB-3111 Dose Reductions for Non-hematologic Toxicity: modified the text of zanubrutinib dose reduction in accordance with corresponding grade of AEs;
- In section 6.5.3, Dose Modification for Rituximab: revised the acceptable rituximab dose delay start time as cycle 4;
- In section 6.6.1, Prior Therapy: revised 'The exclusion criteria specify that patients will not have received prior systemic therapy' to 'The inclusion criteria specify that patients will have received prior systemic therapy';
- In section 6.6.2, Concomitant Therapy: revised the wording for clarification;
- In section 6.6.2.1, Permitted Medications: To add language about the potential for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), in patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, and guidance to consider prophylaxis treatment per institutional standards.
- In section 6.6.3, Potential Interactions Between the Study Drugs and Concomitant Medications and number-updated Appendix 5, CYP3A Inhibitors and Inducers:
  - updated the information of CYP3A inhibitors/inducers as concomitant medications with 'Table 2: Dose Modification Table for Zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers' added (with the following-numbered tables renumbered), based on BGB-3111-104 study;
  - removed the content of concomitant medications that are primarily metabolized by isoenzymes of CYP2C8, CYP2C9 and CYP2C19, based on BGB-3111-108 study (also removed Appendix 7);
  - removed QT/QTc interval prolonging medication and Appendix 5, Medications Which are Known to Prolong the QT Interval and/or Induce Torsades de Pointes (with the following-numbered appendix renumbered), based on BGB-3111-106 study;
  - added the concomitant medications of narrow therapeutic index drugs metabolized by CYP3A4 and CYP2C19.
- In section 6.7, End of Treatment:
  - added 'If a patient underwent study drug interruption > 7 days, before decision of EOT, EOT visit can be done within the interval of 30 ± 3 days after the last dose of study drug,

combining assessments at both EOT and safety Follow-up visits.' for clarification of EOT visit (also in section 7.1.4 and the footnote 4 in Appendix 2);
- replaced 'central review' with 'investigator and medical monitor' in the confirmation of disease progression development;
- added 'Need for long-term' for clarification of prohibited concomitant therapy administration;

- In section 6.8.1, Safety Follow-up: revised the wording as '30 days (±3 days) after the last dose of study drug (zanubrutinib or rituximab, whichever occurs later), or prior to the start of new anticancer therapy, whichever occurs first.' for clarification of safety follow-up period and consistency with other BeiGene protocols;
- In section 6.8.2, Efficacy Follow-up: added 'since Cycle 1 Day 1' and deleted 'new anti-cancer therapy' to specify and correct the period of performing tumor imaging;
- In section 6.8.3, Survival Follow-up: revised the text for clarification of survival follow-up process;
- In section 6.9, End of Study:
  - deleted 'The study will be considered complete once all patients have had disease progression, discontinued treatment due to intolerance, died, withdrew from study, or completed study treatment for a total of 2 years, whichever occurs first' for simplification and clarification;
  - added 'at the time of study closure' to clarify the time point;
- In section 7.1.1, Screening:
  - added 'and disease history' and deleted 'and surgery' to clarify and correct the medical history considered at screening;
  - added IPI score and previous EBER result (if available) in the disease medical history item for exploratory analysis (updated the correlating content also in Appendix 2);
  - added 'for patients with non-GCB DLBCL in cohort 1 while only patients with FL in cohort 2' for clarification of PET scan; (also in section 7.1.4, End of Treatment)
  - deleted 'and pulse oximetry' in vital signs item; (also in section 7.1.2, section 7.1.3, section 7.1.4, and section 7.1.5)

  - deleted ‘must be performed within 3 days of the first dose of zanubrutinib’ in item serum pregnancy test as its unnecessary specification (also in section 7.3.6.6 and the number-updated footnote 18 in Appendix 2);
- In section 7.1.2, section 7.1.3, section 7.1.4 and section 7.1.5: added item Urinalysis, with correlating supplementary information where needs specification;
- In section 7.1.3: added zanubrutinib pre-dose item for supplement in pharmacokinetics blood draw;
- In section 7.1.4, End of Treatment: added ‘for confirmation of progressive disease, if progressive disease is the reason for discontinuation of treatment’ to specify the CT assessment;
- In section 7.1.5, Safety Follow-up: revised the wording for clarification of the safety follow-up period;
- In section 7.2.1.2, PET:
  - added ‘for patients with non-GCB DLBCL and FL until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.’ to specify the appropriate patients on whom perform PET scanning for tumor assessment;
  - added ‘Response assessment for ORR will be by PET scan and categorized as per the Lugano Classification (Appendix 3) for clarification (also revised the schedule of assessment in Appendix 2);
- In section 7.3.1, Adverse Events: revised the wording for correction and clarification of AE/SAE collection period;
- In section 7.3.2: deleted ‘Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient’s eCRF’ for clarification and consistency with the context;
- In section 7.3.5, Electrocardiogram: deleted ‘The Screening ECG should be performed in triplicate’ as in Appendix 2, footnote 10 for duplication in the section;
- In section 7.3.6.2, Clinical Chemistry and Immunoglobulins: added urine test as the replaceable one for BUN test;
- Added section 7.3.6.4, Urinalysis and the corresponding item in Appendix 2 with footnote 15 for clarification of the urine test (with the following-numbered sections and footnotes in Appendix 2 renumbered);

- In section 7.3.6.6, Pregnancy Test: deleted '(within 3 days before the first dose of study drug)' to correct the time performing pregnancy test at screening;
- In section 7.4.1, Biomarker Analysis: added the text of other pathology information for exploratory analysis;
- In section 9.1.1.2, Assessment of Causality: replaced 2-point causality assessment scale for AE causality with 5-point causality assessment based on the actual case;
- In section 9.1.1.3, section 9.6, section 9.7, renumbered section 9.9 and section 9.10: added 'designee' as replaceable role for Sponsor in performing the correlating function;
- In section 9.4.1, Adverse Event Reporting Period: revised the text for clarification and consistency with other BeiGene protocols;
- Removed section 9.9, Adverse Events of Special Interest, and correlating content in section 9.7.1, section 10.3.1 and Table 5 (with the following-numbered section renumbered);
- In section 9.7.2, Completion and Transmission of the Serious Adverse Event Report: deleted telephone notification in the case that both EDC system and facsimile transmission are nonoperational;
- In renumbered section 9.9, Pregnancy Reporting: revised the wording for clarification and correction;
- Removed section 9.10.1, Time Period for Collection Pregnancy Information, with the revised content narrated in section 9.9;
- In section 10, Statistical Methods and Sample Size Determination: deleted the text that is included in the SAP;
- Revised the title of section 10.1.1, Analysis Population as 'Analysis Sets':
  - revised 'Population' as 'Analysis Set' for correction;
  - changed 'any dose' to 'at least 1 dose' for clarification;
  - deleted 'Patients will be assigned to the treatment arms as treated.' for it's a single-arm study;
  - revised 'major protocol deviations' as 'important protocol deviations';
  - revised the wording for clarification of analysis sets for exploratory parameters;
- In section 10.2, Efficacy Data Analysis: added 'TTR' for supplement;
- In section 10.3.1, Adverse Event:

- revised the text for clarification of TEAE definition;
- revised the definition of treatment-related AEs;
- deleted 'Adverse events representing clear evidence of disease progression will not be considered relevant to the assessment of toxicity.' for not relevant to this section;

- In section 10.3.2 and section 10.3.4: deleted 'treatment group' for correction;
- In section 10.3.3, Electrocardiogram: deleted the summarization of ECG change from baseline; for the ECG will only be collected at screening, C1D1 and safety follow-up visit, it doesn't make any sense to summarize change from baseline.;
- In section 10.3.5, Extent of Exposure: revised the wording for correction and clarification;
- In Appendix 2: revised Footnote 2, 4, 7, 8, 10, 18, 19, 21,22, 25 for correction and clarification.

SYNOPSIS

Name of Sponsor/Company:	BeiGene (Beijing) Co., Ltd
Protocol No:	BGB-3111-213
Protocol Title:	A Phase 2 Study to Assess the Safety, Tolerability, and Activity of BGB-3111 in Combination with Rituximab in Chinese Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)
Study Drug:	• Zanubrutinib (also known as BGB-3111) • Rituximab
Phase:	Phase 2
Comparator:	None
Background and Rationale:	Signaling via an aberrantly activated B-cell receptor is known to play a critical role in the pathogenesis of B-cell malignancies by promoting survival and clonal expansion of malignant B-cells. Rituximab, an anti-CD20 monoclonal antibody, is widely used in the treatment of $CD20^+$ B-cell malignancies, both as a component of combination regimens and as single agent, with anti-tumor activity of rituximab dependent in part on antibody-dependent cellular cytotoxicity (ADCC). Phase 2 experiences with ibrutinib in combination with rituximab have demonstrated that the combinations are active, lack overlapping toxicity, and can be combined at full monotherapy doses of the respective agents (Burger et al 2014, Fowler et al 2015, Wang et al 2016). Zanubrutinib is a more potent, more specific second-generation Bruton tyrosine kinase (BTK) inhibitor that has demonstrated a well-tolerated and acceptable safety profile in the ongoing global and China Phase 1 studies (BGB-3111-AU-003 and BGB-3111-1002). Zanubrutinib is more selective against off-target kinases including interleukin-2-inducible T cell kinase (ITK), and is associated with less interference of the ADCC effect induced by anti-CD20 antibodies in pre-clinical studies. In preclinical xenograft models, zanubrutinib has also demonstrated good combination activity with rituximab. In light of the preliminary efficacy and safety data of the ongoing global and China Phase 1 studies of zanubrutinib (BGB-3111-AU-003 and BGB-3111-1002) in B-cell malignancies, the encouraging data of combination zanubrutinib and obinutuzumab, and demonstration of combination activity for zanubrutinib and rituximab in preclinical models, the safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of zanubrutinib in combination with rituximab for non-germinal center B-cell-like (GCB) diffuse large B-cell lymphoma (DLBCL) and indolent lymphoma in Chinese patients will be explored in this study.

Study Design:	This is a Phase 2, multicenter, single-arm, open-label study evaluating the safety and efficacy of zanubrutinib 160 mg twice daily in combination with rituximab in the following patients: Cohort 1 (n=20): relapsed/refractory (R/R) non-GCB DLBCL Cohort 2 (n=20): R/R follicular (FL) or marginal zone lymphoma (MZL) Rituximab will be administered at 375 mg/m^2 intravenously on Cycle 1 Days 1, 8, 15, 22, and on Day 1 of Cycles 4, 6, 8, 10. Zanubrutinib will be administered at 160 mg orally twice daily. Zanubrutinib will be administered at least 30 minutes prior to the initiation of the rituximab infusion. Treatment with zanubrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Rituximab is continued for a total of 8 doses or until disease progression or an unacceptable drug-related toxicity. Patients may withdraw from study treatment due to an adverse event, disease progression, withdrawal of consent. For patients still on study drug at the time of study closure and continuing to benefit from study drug, the Sponsor will make study drug available for continued treatment in a long-term extension study. The continuous safety evaluation of this study will be performed by an internal Safety Monitoring Committee (SMC) as outlined in the SMC charter. Safety evaluation by the SMC will start after 6 patients have completed at least 1 cycle (28 days) of study treatment, and approximately every 6 months to review ongoing safety thereafter according to the progress of study and necessity. Enrollment will be held during the SMC evaluation period (after 6 patients have enrolled) until the SMC has approved re-opening of the trial. Pharmacokinetic blood sampling for zanubrutinib will be performed at (1) pre-dose on Cycle 1 Day 1; (2) 2 hours after zanubrutinib dosing on Cycle 1 Day 1 (± 30 minutes); (3) pre-dose on Cycle 4 Day 1; and (4) 2 hours after zanubrutinib dosing on Cycle 4 Day 1(± 30 minutes). Pharmacokinetics blood sampling for rituximab will be performed at (1) pre-dose on Cycle 1 Day 1; (2) within 30 minutes after end of infusion on Cycle 1 Day 1; (3) pre-dose on Cycle 4 Day 1; (4) within 30 minutes after end of infusion on Cycle 4 Day 1.
Study Duration:	Approximately 2 years from the time of last enrollment until the end of study
Objectives:	All primary and secondary objectives will evaluate zanubrutinib plus rituximab in patients with R/R non-GCB DLBCL, R/R FL, and R/R MZL Primary: • To evaluate efficacy, as measured by overall response rate by investigator

	Secondary: • To evaluate efficacy, as measured by the following: o Duration of response as determined by investigator o Progression-free survival as determined by investigator o Overall survival o Rate of complete response (CR) or complete metabolic response (CMR) as determined by investigator o Time to response as determined by investigator • Safety and tolerability of zanubrutinib in combination with rituximab Exploratory: • To characterize the PK of zanubrutinib in combination with rituximab in patients with R/R non-GCB DLBCL, R/R FL, and R/R MZL • To evaluate the correlation between clinical/genomic risk factors and clinical outcomes in R/R non-GCB DLBCL, R/R FL, and R/R MZL • To explore mechanisms of disease resistance in samples from patients who fail to achieve partial response (PR) or better after at least 6 months of study treatment, and from those who manifest disease relapse in R/R non-GCB DLBCL, R/R FL, and R/R MZL
Planned Number of Patients:	Approximately 40
Study Population:	**Inclusion Criteria:** 1. Age ≥ 18 years at time of signing of informed consent. 2. Measurable disease by computed tomography (CT) or positron emission tomography (PET)/CT or magnetic resonance imaging (MRI), defined as ≥ 1 nodal lesion that is > 1.5 cm in the longest diameter, or ≥ 1 extra-nodal lesion (eg, hepatic nodules) that is > 1 cm in the longest diameter. 3. Availability of archival or a fresh tumor tissue sample from an evaluable core or excisional biopsy (paraffin embedded block or 10-15 unstained formalin-fixed paraffin-embedded [FFPE] slides) to meet the requirement of biomarker analysis. 4. Patients meet the following criteria: a. Cohort 1: R/R non-GCB DLBCL i. Histologically confirmed non-GCB DLBCL per Hans criteria (Hans et al 2004) with non-transformed

disease; additional methodologies for confirming non-GCB DLBCL may be considered in consultation with the medical monitor

ii. Relapsed disease (disease progression after most recent therapy for DLBCL occurring more than 6 months after the completion of last therapy) or refractory disease (failure to achieve CR or partial response [PR] to therapy for non-GCB DLBCL or disease progression within 6 months after completion of the most recent therapy for non-GCB DLBCL)

iii. Must have received at least one standard anthracycline ± rituximab-based treatment (eg, R-CHOP) or CVP ± R for DLBCL

b. Cohort 2: R/R FL or R/R MZL

i. Histologically confirmed $CD20^+$ FL (Grade 1, 2, or 3a) or MZL

ii. Relapsed disease (disease progression after most recent therapy for FL or MZL occurring more than 6 months after the completion of last therapy) or refractory disease (failure to achieve CR or PR to most recent therapy for FL or MZL, or disease progression within 6 months after completion of the most recent therapy for FL or MZL)

5. Laboratory parameters as specified below:

a. Hematologic: Platelet count ≥ 75 x 10^9/L independent of growth factor or transfusion within 7 days of study entry; absolute neutrophil count (ANC) ≥ 1 x 10^9/L independent of growth factor within 7 days of study entry, hemoglobin (Hgb) > 8 g/dL within 7 days of study entry

b. Hepatic: Total bilirubin ≤ 2x upper limit of normal (ULN) unless documented Gilbert's syndrome; aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤ 3 x ULN

c. Renal: Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation based on ideal body weight or as measured by nuclear medicine scan or 24-hour urine collection)

	d. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Patients with anti-phospholipid syndrome, acquired von Willebrand disease, factor inhibitors or on vitamin K antagonist may be enrolled after discussion with the medical monitor 6. Left ventricular ejection fraction (LVEF) ≥ 50%. 7. Life expectancy ≥ 6 months. 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. 9. Female patients of childbearing potential must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, or 12 months after the last dose of rituximab, whichever is longer. These methods include the following: a. Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation i. Oral, intravaginal or transdermal b. Progestogen-only hormonal contraception associated with the inhibition of ovulation i. Oral, injectable, implantable c. An intrauterine device d. Intrauterine hormone-releasing system e. Bilateral tubal occlusion f. Vasectomized partner g. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib or 12 months after the last dose of rituximab). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception. Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this

method must be used in combination with another acceptable method listed above.

10. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception in combination with other methods above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib.

11. Able to provide written informed consent and can understand and comply with the requirements of the study.

Exclusion Criteria:

1. Known central nervous system lymphoma or leukemia.

2. Histological confirmed gastric mucosa-associated lymphoid tissue (MALT) type MZL.

3. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.

4. Clinically significant cardiovascular disease including the following:

    a. Myocardial infarction within 6 months before screening

    b. Unstable angina within 3 months before screening

    c. New York Heart Association Class III or IV congestive heart failure

    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)

    e. QT interval corrected using Fridericia's formula (QTcF) > 480 msecs based on Fredericia's formula

    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place

    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening

5. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention.

6. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.

7. Severe or debilitating pulmonary disease.

	8. Hypersensitivity reaction to zanubrutinib or rituximab or any of the other ingredients of the study drugs. 9. Prior BTK inhibitor treatment. 10. Requires ongoing treatment with a strong Cytochrome P450 3A (CYP3A) inhibitor or inducer (see Appendix 5). 11. Vaccination with a live vaccine within 28 days of the first dose of study drug. 12. Hematopoietic stem cell transplantation within 6 months of first dose of study drug. 13. Receipt of the following treatment prior to first dose of study drug: a. Corticosteroids at doses >20 mg/day prednisone equivalent or steroids given with anti-neoplastic intent within 7 days prior to first dose of study drug. b. Chemotherapy or radiotherapy within 4 weeks. c. Monoclonal antibody within 4 weeks. d. Investigational therapy within 4 weeks. e. Chinese patent medicine with anti-neoplastic intent within 4 weeks. 14. Not recovered from toxicity of any prior anti-cancer therapy to ≤ Grade 1, except for alopecia, ANC, Hgb and platelets. For ANC, Hgb and platelets, see Inclusion criterion #5. 15. Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast. 16. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, history of bariatric surgery, or partial or complete bowel obstruction. 17. Major surgery within 4 weeks prior to first dose of study treatment. 18. Active fungal, bacterial and/or viral infection requiring systemic therapy. 19. Known infection with human immunodeficiency virus (HIV), or

	serologic status reflecting active hepatitis B or C infection as follows: a. Presence of hepatitis B surface antigen (HBsAg) or anti-hepatitis B core antibody (anti-HBc). Patients with presence of anti-HBc, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is < 500 IU/mL; anti-viral therapy will be started before the first dose of study drug, and maintained throughout the study treatment with monthly monitoring for HBV reactivation. b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (<15 IU/mL). See Section 7.3.6.5 and Table 4 for more information. 20. Pregnant or lactating women. 21. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs. 22. Concurrent participation in another therapeutic clinical trial.
Test Product, Dose, and Mode of Administration:	• Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food at approximately the same time starting from Cycle 1 Day 1. The capsules should be taken approximately 12 hours apart, ± 2 hour time window. On days where both study drugs are administered, zanubrutinib will be given first and 30 minutes later, the infusion of rituximab will be initiated. • Rituximab will be administered intravenously at a dose of 375 mg/m^2 in accordance with the Prescribing Information dose for NHL. There is a front loading four-weekly infusion of rituximab in Cycle 1 during time of initial highest disease burden, followed by infusions on Day 1 of Cycles 4, 6, 8, and 10.
Study Assessments:	Response will be assessed by computed tomography (CT) scan and categorized as per the Lugano Classification (Cheson et al 2014). Tumor assessment by CT with contrast of neck, chest, abdomen, and pelvis will be performed at protocol specified time points. CT scan with contrast will occur at Screening, Week 12, and every 12 weeks thereafter until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Total body MRI is allowed if CT with contrast is contraindicated. Positron emission tomography (PET)/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered.

	Tumor assessment by PET scan will be performed at Screening, Week 24, Week 48, progressive disease suspected clinically or by CT (MRI if CT contraindicated), and CR suspected clinically or by CT (MRI if CT contraindicated), for sites with PET scanning capability, until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Safety assessments should be performed at all visits by the investigator throughout the study. Safety assessments will consist of monitoring all adverse events (AEs) and serious AEs (SAEs), regular monitoring of blood tests, urine tests, vital signs, weight, ECOG performance status, and physical examinations. Patients will be evaluated for AEs (all grades per the National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4.03 [NCI-CTCAE Version 4.03]), SAEs and any AEs requiring study drug interruption or discontinuation, starting from Screening until 30 days after last dose of zanubrutinib or 90 days after the last dose of rituximab, whichever is longer. For schedule of study visits, refer to Appendix 2, Schedule of Assessments.
Concomitant medications:	• Patients with high tumor burden should be monitored closely and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards. Tumor lysis syndrome has not been currently reported with zanubrutinib treatment, but has been reported in some cases with rituximab. • Bisphosphonate use is permitted if the patient has already been on it for 3 or more months and on a stable dose. • Corticosteroid courses of limited duration (2 weeks or less) and dose (<20 mg prednisone per day, or equivalent) are permitted, if used to treat a concomitant (non-cancer) medical condition, with the exception of glucocorticoids used for management of rituximab-related infusion reaction. • Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards. • Patients should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement) while on treatment in this study.

	• Other anticancer therapy should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the study drug. • Chinese patent medicine for treatment of cancer are not allowed on study. Chinese herbal medications in the use of anti-cancer treatment is prohibited • Live vaccines are prohibited during Screening and while on study treatment. • Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 5 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and should consider using alternative agents. If these agents will be used, follow the dose modification instruction in Table 2. The medical monitor should be consulted in these situations. Please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers 2019 for a more complete list. • Clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Since blood levels and effectiveness of drugs that are substrates for CYP3A (eg, steroidal contraceptives) may be reduced by CYP3A inducers, if patients are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) is recommended to be used. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.
Study Endpoints:	Primary Endpoint: • Overall response rate (ORR) as measured by investigator Secondary Endpoints: • Duration of response as determined by investigator

	• Progression-free survival as determined by investigator • Overall survival • Rate of complete response or complete metabolic response as determined by investigator • Time to response as determined by investigator • Safety and tolerability of zanubrutinib in combination with rituximab as evaluated by the incidence and severity of AEs, clinical laboratory abnormalities, deaths and cause of death Exploratory Endpoints: [redacted]
Statistical Methods:	The analyses for both efficacy and safety endpoints will be performed in the Safety Analysis Set defined as all patients who received at least 1 dose of zanubrutinib or rituximab on the study. The primary endpoint of ORR will be determined by the crude proportion as crude proportion (number of patients who achieve PR or higher) as best response. The estimate of ORR with 95% exact confidence interval will be presented in each cohort. CR and CMR will be analyzed using the same methods applied for ORR analysis. Listings for time to event secondary efficacy endpoints (progression-free survival [PFS], duration of response [DOR], overall survival [OS], and time to response) will be generated. The distribution of time to event secondary efficacy endpoints will be estimated where applicable. All patients for whom valid zanubrutinib PK can be estimated and no important protocol deviations affecting PK will be included in the PK Analysis Set on an as treated basis. Similarly, patients for whom valid rituximab PK can be estimated and no important protocol deviations affecting PK will be included in the PK Analysis Set on an as treated basis. For exploratory parameters, all patients for whom can be estimated on with evaluable data will be included in the summaries. All safety and tolerability data recorded during the study will be listed and summarized as appropriate. Continuous variables will be summarized using descriptive statistics and by time points where applicable. Categorical variables will be summarized in frequency tables.

	The sample size is 20 for each cohort, totaling 40 for the study. No formal statistical hypothesis testing will be performed for study endpoints and the sample size was not determined by statistical power consideration.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
BTK	Bruton tyrosine kinase
CBC	complete blood count
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMR	complete metabolic response
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 protein
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FL	follicular lymphoma
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
ICH	International Conference on Harmonization
IEC	independent ethics committee

Ig	immunoglobin
IND	Investigational New Drug
IRB	Institutional Review Board
ITK	interleukin-2-inducible T cell kinase
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	Multigated acquisition scan
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
R/R	relapsed/refractory
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
WM	Waldenström macroglobulinemia
zanubrutinib	BGB-3111

1 INTRODUCTION

Bruton tyrosine kinase (BTK), a member of the non-receptor tyrosine kinases that include BTK/AKT, tyrosine kinase expressed in hepatocellular carcinoma (TEC), interleukin-2-inducible T cell kinase (ITK)/EMT/TSK, and Bone marrow tyrosine kinase gene in Chromosome X protein (BMX)/epithelial and endothelial tyrosine kinase (ETK), is a critical component of the B-cell receptor signaling cascade. The defining features of these kinases is the presence of a pleckstrin homology domain at their N-terminus. Bruton tyrosine kinase has a restricted expression in a subset of B-cells and in myeloid cells, and is involved in signaling by B-cell antigen receptor, mast cell FcεR, interleukin (IL)-5; IL-6 receptor. Naturally occurring mutations of BTK were initially identified in the human immunodeficiency disease X-linked agammaglobulinemia (XLA) and murine X-linked immunodeficiency. The XLA phenotype includes the lack of mature circulating B-cells and immunoglobulins (Qiu and Kung 2000).

Antigen binding to B-cell receptor immunoglobulin heavy chains and light chains triggers activation of immunoreceptor tyrosine-based activation motifs in CD79A and CD79B with subsequent phosphorylation of spleen tyrosine kinase. Spleen tyrosine kinase recruits B-cell linker protein which, in turn, phosphorylates BTK and phospholipase C-gamma-2 (PLCγ2). In addition, SRC-family kinases activated through IgH and IgL binding also phosphorylate CD19 which recruits PI3K to the B-cell receptor. These signals ultimately translate into nuclear factor-κB and AKT activation, promoting proliferation and survival of normal and malignant B-cells (Blum 2015). Inhibition of BTK has emerged as a promising strategy for B-cell malignancies (Blum 2015, Young and Staudt 2013).

Ibrutinib, a first generation small-molecule BTK inhibitor, has demonstrated activity in several B-cell malignancies including mantle cell lymphoma (MCL) (Tucker and Rule 2016, Wang et al 2016), chronic lymphocytic leukemia (CLL) (Burger et al 2014, Byrd et al 2013), Waldenström macroglobulinemia (WM) (Castillo et al 2016, Dimopoulos et al 2017), follicular lymphoma (FL) (Fowler et al 2015, Ujjani et al 2016), multiple myeloma (Naymagon and Abdul-Hay 2016), and activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) (Wilson et al 2015). Ibrutinib acts by forming a stable covalent bond to the amino acid cysteine at position 481 in the BTK active site, consequently blocking adenosine triphosphate from binding and thus preventing activation of BTK (Gayko et al 2015). Adverse reactions with ibrutinib treatment,

believed to be related to ibrutinib's off-target activities against epidermal growth factor receptor (EGFR)/Janus kinase (JAK)3/TEC, include skin rash, nausea, vomiting, thrombocytopenia, bleeding, and atrial fibrillation. It is currently approved by the United States (US) Food and Drug Administration (FDA) for treatment of patients with MCL who had received at least one prior therapy, CLL/small lymphocytic lymphoma (SLL) with or without 17p deletion, WM, and marginal zone lymphoma (MZL) who had received at least one prior anti-CD20-based therapy (Imbruvica USPI).

1.1 Zanubrutinib

Zanubrutinib (BGB-3111) is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacologic/toxicologic profile. Preclinical data suggests that zanubrutinib is differentiated from ibrutinib in the following aspects:

(1) Zanubrutinib is more selective than ibrutinib in the inhibition of BTK versus EGFR, Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), Fyn-related kinase (FRK), human epidermal growth factor receptor (HER)2, HER4, ITK, JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and tyrosine kinase expressed in TEC. The predicted efficacious dose of zanubrutinib in patients is much lower than ibrutinib. Accordingly, off-target kinase inhibition potentially associated with common, and occasionally severe, adverse effects associated with ibrutinib therapy, such as thrombocytopenia, bleeding, atrial fibrillation, rash, and gastrointestinal toxicities, may be reduced relative to ibrutinib;

(2) Zanubrutinib has better oral bioavailability than ibrutinib;

(3) Due to its weaker ITK inhibitory activity, zanubrutinib displays a significantly less inhibitory effect on rituximab-induced antibody dependent cell-mediated cytotoxicity (ADCC) compared to ibrutinib in preclinical studies (Da Roit et al 2015, Hans et al 2004), and is therefore unlikely to adversely impact the anti-tumor effects of rituximab.

1.1.1 Summary of Relevant Non-clinical Data with zanubrutinib

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

Zanubrutinib is a potent, specific and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomole per litre (nM). Cellular assays confirm that zanubrutinib inhibits B-cell receptor aggregation-triggered BTK autophosphorylation, and blocks downstream PLCγ2 signaling in mantle cell lymphoma cell lines. Zanubrutinib had an IC_{50} of 1.8 nM in a homogeneous time resolved fluorescence-based BTKpY223 assay. It potently and selectively inhibited cellular growth of several mantle cell lymphoma cell lines (REC-1, Mino and JeKo-1) and the activated B-cell type diffuse large B-cell lymphoma cell line transmembrane domain 8 (TMD-8), with IC_{50} values from 0.36 nM to 20 nM, while it was inactive in many other hematologic cancer cell lines.

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

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

Cytochrome P450 (CYP) phenotyping in human liver microsomes suggests that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism. Zanubrutinib is a weak, reversible inhibitor of CYP2C8 and intestinal (but not hepatic) CYP3A4, and does not display clinically relevant time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Zanubrutinib is a weak inducer of CYP2B6 and CYP3A4, but does not induce CYP1A2.

Although zanubrutinib is a sensitive CYP3A4 substrate, it does not have a clinically relevant effect on its own exposure. Zanubrutinib may inhibit breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) transport at clinical doses. When co-administrated with zanubrutinib, the exposure of narrow therapeutic window P-gp or BCRP substrated (eg, digoxin, methotrexate) may increase. Zanubrutinib does not inhibit the hepatic uptake transporters, OATP1B1 and OATP1B3, or the renal uptake transporters, organic anion transporter (OAT) 1, OAT2, and organic cation transporter (OCT) 2.

The toxicity profiles of zanubrutinib have been well characterized in rats and dogs. No specific safety concerns were identified in vital organs/systems including cardiovascular system, respiratory system, and central nervous systems. No corrected QT interval (QTc) changes were noted in the conscious telemetry implanted dogs over 24 hours after dosing up to 100 mg/kg, or in the repeat dose toxicity studies in dogs over 91 days at doses up to 100 mg/kg/day. No mortality or severe toxicity was noted in 91-day repeat-dose toxicity studies in both rats and dogs at doses up to 300 mg/kg and 100 mg/kg, respectively. Test article-related reversible histopathology changes were mainly noted in rats, including pancreas, spleen, prostate gland, cecum, colon, rectum, skin (lip and/or nose), and uterus. None of the above findings were considered to be adverse in the 91-day repeated dosing studies. No genotoxicity was noted in the genotoxicity core battery studies.

1.1.2 Dose Selection for zanubrutinib

In the first-in-human (FIH), phase 1 study, BGB-3111-AU-003, the PK of BGB-3111 was linear between 40 mg and 320 mg daily administered orally (BGB-3111 Investigator's Brochure). The absorption of zanubrutinib is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 4 hours at 320 mg daily. Results from a food effect study showed that zanubrutinib exposure was not altered by a high-fat breakfast, and mean area under the concentration-time curve (AUC) and maximum observed 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 daily in the ongoing phase 1, and was not associated with any new safety findings. Therefore, zanubrutinib can be administered with or without food. The terminal elimination half-life is approximately 4 hours at 320 mg daily.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the

BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice daily and 320 mg daily (Tam et al 2015). At the 160 mg twice a day dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including CLL, MCL, WM and FL) at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive research at the 160 mg twice daily and 320 mg daily dose; both schedules show a high level of activity without compromise of the tolerability profile as compared to lower doses of zanubrutinib. Therefore, the dose of 160 mg administered orally twice a day has been selected as the recommended phase 2 and phase 3 dose based on sustained target occupancy, high rates of objective response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

Rituximab is administered intravenously at 375 mg/m^2 in accordance with the US Prescribing Information dose for NHL. There is a front loading, four-weekly infusion of rituximab in Cycle 1 during time of initial highest disease burden, followed by infusions on Day 1 of Cycles 4, 6, 8, and 10.

1.1.3 Preliminary Efficacy Data with zanubrutinib

In the FIH study of zanubrutinib (BGB-3111-AU-003), the first patient, first visit occurred on 25 August 2014. Of the 54 CLL/SLL patients evaluable for response (>12 weeks follow-up or discontinuation before 12 weeks) as of 15 December 2016, the objective response rate was 96% (52/54), with partial response (PR) in 67% (36/54), PR with lymphocytosis in 30% (16/54), stable disease in 1 relapsed/refractory (R/R) patient, and no assessment for 1 R/R patient because of adverse event (AE). No instances of disease progression or Richter transformation were reported.

As of 31 December 2016, 41 patients with WM were evaluable for efficacy (5 non-evaluable patients had either baseline IgM <500 mg/dL [n=3] recent plasmapheresis [n=1] or <12 weeks' follow-up [n=1]). The objective response rate was 93% (38/41), with a major response rate of 78% (32/41): very good partial response (VGPR) in 39% (16/41) and PR in 39% (16/41). Median time to response was 28 days. The sole patient with disease progression remains on zanubrutinib with ongoing clinical benefit.

BGB-3111-1002 is the Phase I study in China and the first patient, first visit occurred on 05 July 2016. The efficacy data for this study are not yet available for analysis.

BGB-3111-GA101_Study_001 is the combination study of zanubrutinib and obinutuzumab. The first patient visit occurred on 22 December 2015. As of 15 December 2016, 40 patients with CLL/SLL (17 patients with treatment-naive [TN]; 23 patients with R/R), and 13 patients with FL were enrolled. Patients were evaluable for response if they had completed baseline and ≥1 on-treatment response assessment. Objective response rates (complete response [CR] + PR+ PR with lymphocytosis) were 88.9%, 86.7%, and 81.8% in TN CLL/SLL, R/R CLL/SLL, and R/R FL, respectively, with 3 CRs in R/R CLL/SLL and 5 CRs in FL. Two patients (1 R/R CLL;1 FL) experienced disease progression; no instances of disease transformation occurred.

1.1.4 Preliminary Safety Data with zanubrutinib

Preliminary results from the FIH BGB-3111 study have demonstrated that zanubrutinib is well tolerated in patients with advanced B-cell malignancies. As of 15 December 2016, 68 patients with CLL/SLL (50 R/R and 18 TN) were enrolled in the Phase 1 Study. The median follow-up was 7.2 months (range, 0-23.3). The most frequent adverse events (AEs) of any cause were bruising (35%) and petechiae (11%), upper respiratory tract infection (28%), fatigue (25%), cough (22%), and diarrhea (21%). Four serious AEs (SAEs) related to zanubrutinib were seen in 3 patients: Grade 2 cardiac failure, Grade 2 pleural effusion, Grade 3 purpura, and Grade 3 pneumonia. The case of Grade 3 purpura (subcutaneous hemorrhage) was the only major bleeding event reported. Atrial fibrillation (Grade 3) occurred in 1 patient. One patient discontinued zanubrutinib for an AE (pleural effusion). As of 31 December 2016, 46 patients with WM were enrolled and evaluable for safety: median 2 prior therapies (range 0-8), median follow-up 8.2 months (1.4-28). The most frequent AEs (≥20%, all Grade 1 or 2) were upper respiratory infection (33%), contusion (28%), and constipation (22%). There were 3 treatment-related SAEs (Grade 2 atrial fibrillation [AF], Grade 2 headache, Grade 3 cryptococcal meningitis); in all 3 cases, zanubrutinib was withheld and safely resumed. Three patients developed AF (one Grade 1, two Grade 2), and 1 developed Grade 3 diarrhea. No serious hemorrhage was reported.

Of the 21 patients enrolled in BGB-3111-1002 as of the October 2016 data cutoff, 12 patients (57%) had experienced a treatment-emergent adverse event (TEAE) of >Grade 2 severity. Additionally, 18/21 (86%) of all patients had experienced a TEAE assessed by the investigator as related to

treatment. There had been no SAEs, AEs leading to discontinuation, or fatal AEs.

For BGB-3111-GA101_Study_001, BGB-3111 plus obinutuzumab was well tolerated. As of 15 December 2016, no fatal AEs occurred; only 1 AE led to treatment discontinuation (squamous cell carcinoma in a patient with prior squamous cell carcinoma). SAEs were reported in 25.0% of CLL/SLL patients and 23.1% of FL patients; there was only 1 SAE related to obinutuzumab (infusion-related reaction) and 1 SAE related to zanubrutinib (pneumonia). There were no AEs of atrial fibrillation.

1.1.5 Clinical Pharmacology

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

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that, in healthy volunteers, co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once daily for 8 days) decreased exposure of zanubrutinib by 13.5-fold for area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), and 12.6-fold for C_{max}. Co-administration of zanubrutinib with strong CYP3A inhibitor itraconazole (200 mg once daily for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

Based on the in vitro study, a clinical drug-drug interaction study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), BCRP (rosuvastatin) using a cocktail approach. The study showed that zanubrutinib has no effect on CYP2C9 enzyme and BCRP activity. Zanubrutinib is shown to be a mild CYP3A4 and CYP2C19 inducer per FDA guidelines. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib. Repeated dosing of

zanubrutinib increased exposure of digoxin (P-gP substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}.

1.2 Rituximab

Rituximab is a genetically engineered, chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Rituximab has an approximate molecular weight of 145 kilodalton (kD), and a binding affinity for the CD20 antigen of approximately 8.0 nM. Upon binding to CD20, rituximab mediates B-cell lysis, with possible mechanisms of lysis including complement-dependent cytotoxicity (CDC) and ADCC. The antibody induced apoptosis in the SU-DHL 4 human B-cell lymphoma cell line. In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Circulating CD19-positive B cells are depleted within the first three weeks with sustained depletion for up to 6 to 9 months after rituximab treatment in 83% of patients. B-cell recovery begins at approximately 6 months, and median B-cell levels return to normal by 12 months following completion of treatment. Rituximab can be detectable in serum of patients 3 to 6 months after treatment cessation (Rituxan USPI).

Based on population PK analysis of data from 298 non-Hodgkin lymphoma (NHL) patients who received rituximab once weekly or once every 3 weeks, the estimated median terminal elimination half-life is 22 days (range 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pre-treatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender have no effect on the PK of rituximab (Rituxan USPI).

Most common AEs associated with rituximab treatment in clinical trials for NHL were infusion reaction, fever, lymphopenia, chills, infection, and asthenia. For CLL, most common AEs were infusion reaction and neutropenia. Severe mucocutaneous reaction, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy have also been reported with rituximab treatments. Tumor lysis syndrome (TLS) can be associated with rituximab treatment in patients with NHL, with a high number of circulating malignant cells ($\geq 25{,}000/mm^3$) or high tumor burden conferring a greater risk of TLS (Rituxan USPI).

Rituximab is currently approved in the US for treatment of $CD20^+$ NHL, CLL, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis.

1.3 Study Rationale

Signaling via an aberrantly activated B-cell receptor is known to play a critical role in the pathogenesis of B-cell malignancies by promoting survival and clonal expansion of malignant B-cells. Treatment with inhibitors of BTK such as ibrutinib has demonstrated responses in patients with various B-cell malignancies including CLL/SLL, MCL, DLBCL, FL, MZL, and WM.

Rituximab, an anti-CD20 monoclonal antibody, is widely used in the treatment of $CD20^+$ B-cell malignancies, both as a component of combination regimens and as single agent, with anti-tumor activity of rituximab dependent in part on ADCC. Phase 2 experiences with ibrutinib in combination with rituximab have demonstrated that the combinations are active, lack overlapping toxicity, and can be combined at full monotherapy doses of the respective agents (Burger et al 2014, Fowler et al 2015, Wang et al 2016).

Zanubrutinib, compared to ibrutinib, is a more potent, more specific second-generation BTK inhibitor that has demonstrated a well-tolerated and acceptable safety profile in the ongoing global and China Phase 1 studies (BGB-3111-AU-003 and BGB-3111-1002). Furthermore, compared to ibrutinib, zanubrutinib is more selective against off-target kinases including ITK, and is associated with less interference of the ADCC effect induced by anti-CD20 antibodies in pre-clinical studies. In preclinical xenograft models, zanubrutinib has also demonstrated good combination activity with rituximab.

In light of the preliminary efficacy and safety data of the ongoing global and China Phase 1 studies of zanubrutinib (BGB-3111-AU-003 and BGB-3111-1002) in B-cell malignancies, the encouraging data of combination ibrutinib and rituximab, and demonstration of combination activity for zanubrutinib and rituximab in preclinical models, the preliminary efficacy as well as safety, tolerability, and PK of zanubrutinib in combination with rituximab for non-Hodgkin lymphoma in Chinese patients will be explored in this study.

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

2 OBJECTIVES

All primary and secondary objectives will evaluate zanubrutinib plus rituximab in patients with relapsed/refractory (R/R) non-germinal center B-cell-like (GCB) DLBCL, R/R FL, and R/R MZL.

2.1 Primary Objective

- To evaluate efficacy, as measured by overall response rate (ORR) by investigator

2.2 Secondary Objectives

- To evaluate efficacy, as measured by the following:
    - Duration of response as determined by investigator
    - Progression-free survival as determined by investigator
    - Overall survival
    - Rate of complete response or complete metabolic response as determined by investigator
    - Time to response as determined by investigator
- Safety and tolerability

2.3 Exploratory Objectives

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- Overall response rate (ORR) measured by investigator

3.2 Secondary Endpoints

- Duration of response as determined by investigator
- Progression-free survival as determined by investigator
- Overall survival
- Rate of complete response or complete metabolic response as determined by investigator
- Time to response as determined by investigator
- Safety and tolerability of zanubrutinib in combination with rituximab as evaluated by the incidence and severity of AEs, clinical laboratory abnormalities, deaths and cause of death

3.3 Exploratory Endpoints

[redacted]

4 STUDY DESIGN

This is a multicenter open-label study evaluating the safety and efficacy of zanubrutinib 160 mg twice daily in combination with rituximab in the following patients:

Cohort 1 (n=20): relapsed/refractory non-GCB DLBCL

Cohort 2 (n=20): relapsed/refractory FL or MZL

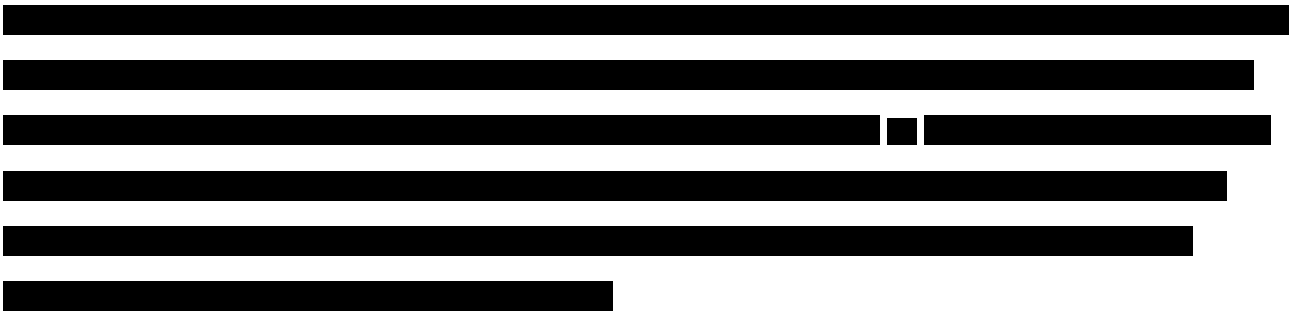
Rituximab will be administered at 375 mg/m^2 intravenously on Cycle 1 Days 1, 8, 15, 22, and on Day 1 of Cycles 4, 6, 8, 10.

Zanubrutinib will be administered at 160 mg orally twice daily. Zanubrutinib will be administered at least 30 minutes prior to the initiation of the rituximab infusion.

Treatment with zanubrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Rituximab is continued for a total of 8 doses or until disease progression or an unacceptable drug-related toxicity. Patients may withdraw from study treatment due to an adverse event, disease progression, withdrawal of consent. For patients still on study drug at the time of study closure and continuing to benefit from study drug, the Sponsor will make study drug available for continued treatment in a long-term extension study.

The continuous safety evaluation of this study will be performed by a Safety Monitoring Committee (SMC) as outlined in the SMC charter.

Safety evaluation by the SMC will be performed after 6 patients have completed at least 1 cycle (28 days) of study treatment, and approximately every 6 months to review ongoing safety thereafter or according to the progress of study and necessity. Enrollment will be held during the SMC evaluation period (after 6 patients have enrolled) until the SMC has approved re-opening of the trial.



4.1 Duration of Study

The total duration of this study is expected to be approximately 3 years, assuming an expected enrollment duration of 12 months and completed study treatment for a total of 24 months after the last enrolled patient. All patients in the study will receive zanubrutinib and rituximab for Cycles 1 to 10, then single agent zanubrutinib for up to 2 years total treatment from Cycle 1 Day 1, until disease

progression, unacceptable toxicity or death, withdrawal of consent, or the study is terminated by the Sponsor for final analysis. Patients continuing to benefit after study closure will be given the opportunity to continue to receive single agent zanubrutinib on a long-term extension study.

5 STUDY POPULATION

Approximately 40 patients will be enrolled.

5.1 Inclusion Criteria

Patients may be enrolled on study only if they meet all the following criteria:

1. Age ≥ 18 years at time of signing of informed consent.
2. Measurable disease by computed tomography (CT) or positron emission tomography (PET)/CT or magnetic resonance imaging (MRI), defined as ≥ 1 nodal lesion that is > 1.5 cm in the longest diameter, or ≥ 1 extra-nodal lesion (eg, hepatic nodules) that is > 1 cm in the longest diameter.
3. Availability of archival or a fresh tumor tissue sample from an evaluable core or excisional biopsy (paraffin embedded block or 10-15 unstained formalin-fixed, paraffin-embedded [FFPE] slides) to meet the requirement of biomarker analysis
4. Patients meet the following criteria:
    a. Cohort 1: R/R non-GCB DLBCL
        i. Histologically confirmed non-GCB DLBCL per Hans criteria (Hans et al 2004) with non-transformed disease
        ii. Relapsed disease (disease progression after most recent therapy for DLBCL occurring more than 6 months after the completion of last therapy) or refractory disease (failure to achieve CR or PR to therapy for non-GCB DLBCL or disease progression within 6 months after completion of the most recent therapy for non-GCB DLBCL)

iii. Must have received at least one standard anthracycline ± rituximab-based treatment (eg, R- CHOP) or CVP+/- R for DLBCL

b. Cohort 2: R/R FL or R/R MZL

i. Histologically confirmed CD20+ FL (Grade 1, 2, or 3a) or MZL

ii. Relapsed disease (disease progression after most recent therapy for FL or MZL occurring more than 6 months after the completion of last therapy) or refractory disease (failure to achieve CR or PR to most recent therapy for FL or MZL, or disease progression within 6 months after completion of the most recent therapy for FL or MZL).

5. Laboratory parameters as specified below:

a. Hematologic: Platelet count ≥ 75 x 10^9/L independent of growth factor or transfusion within 7 days of study entry; absolute neutrophil count (ANC) ≥ 1 x 10^9/L independent of growth factor within 7 days of study entry, hemoglobin (Hgb) > 8 g/dL within 7 days of study entry.

b. Hepatic: Total bilirubin ≤ 2x upper limit of normal (ULN) unless documented Gilbert's syndrome; aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤ 3x ULN.

c. Renal: Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation based on ideal body weight or as measured by nuclear medicine scan or 24-hour urine collection)

d. International normalized ratio and activated partial thromboplastin time (aPTT) ≤ 1.5x ULN. Patients with anti-phospholipid syndrome, acquired von Willebrand disease, factor inhibitors or on vitamin K antagonist may be enrolled after discussion with the Medical Monitor.

6. Left ventricular ejection fraction (LVEF) ≥ 50%.

7. Life expectancy ≥ 6 months.

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

9. Female patients of childbearing potential must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, or 12 months after the last dose of rituximab, whichever is longer. These methods include the following:

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

        i. Oral, intravaginal or transdermal

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

        i. Oral, injectable, implantable

    c. An intrauterine device

    d. Intrauterine hormone-releasing system

    e. Bilateral tubal occlusion

    f. Vasectomized partner

    g. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib or 12 months after the last dose of rituximab). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.
    Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above.

10. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception in combination with other methods above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib.

11. Able to provide written informed consent and can understand and comply with the requirements of the study.

5.2 Exclusion Criteria

1. Known central nervous system lymphoma or leukemia.
2. Histological confirmed gastric mucosa-associated lymphoid tissue (MALT) type MZL.
3. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
4. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within 6 months before screening
    b. Unstable angina within 3 months before screening
    c. New York Heart Association class III or IV congestive heart failure
    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    e. QT interval corrected using Fridericia's formula (QTcF) > 480 msecs based on Fredericia's formula
    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening
5. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention.

6. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
7. Severe or debilitating pulmonary disease.
8. Hypersensitivity reaction to zanubrutinib or rituximab or any of the other ingredients of the study drugs.
9. Prior BTK inhibitor treatment.
10. Requires ongoing treatment with a strong CYP3A inhibitor or inducer (see Appendix 5).
11. Vaccination with a live vaccine within 28 days of the first dose of study drug.
12. Hematopoietic stem cell transplantation within 6 months of first dose of study drug.
13. Receipt of the following treatment prior to first dose of study drug:
    a. Corticosteroids at doses >20 mg/day prednisone equivalent or steroids given with anti-neoplastic intent within 7 days prior to first dose of study drug.
    b. Chemotherapy or radiotherapy within 4 weeks.
    c. Monoclonal antibody within 4 weeks.
    d. Investigational therapy within 4 weeks.
    e. Chinese patent medicine with anti-neoplastic intent within 4 weeks.
14. Not recovered from toxicity of any prior anti-cancer therapy to ≤ Grade 1, except for alopecia, ANC, Hgb and platelets. For ANC, Hgb and platelets, see Inclusion criterion #5.
15. Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast.
16. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, history of bariatric surgery, or partial or complete bowel obstruction.
17. Major surgery within 4 weeks prior to first dose of study treatment.

18. Active fungal, bacterial and/or viral infection requiring systemic therapy.

19. Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or C infection as follows:

    a. Presence of hepatitis B surface antigen (HBsAg) or anti-hepatitis B core antibody (anti-HBcAb). Patients with presence of anti-HBcAb, but absence of HBsAg, are eligible if HBV DNA is < 500 IU/mL; anti-viral therapy will be started before the first dose of study drug, and maintained throughout the study treatment with monthly monitoring for HBV reactivation.

    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (<15 IU/mL).
    See Section 7.3.6.5 and Table 4 for more information.

20. Pregnant or lactating women.

21. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs.

22. Concurrent participation in another therapeutic clinical trial.

6 STUDY TREATMENTS

6.1 Study Treatment

All patients will receive zanubrutinib in combination with rituximab from Cycles 1 to 10, followed by zanubrutinib monotherapy starting at Cycle 11.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

Supplies of zanubrutinib capsules will be provided in a child resistant, high-density polyethylene (HDPE) bottle with induction seal and bottle label. Rituximab will be provided in vials containing solution for infusion.

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

6.2.2 Handling and Storage

The study drugs will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the Sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel, and kept under physical conditions per the product label requirements.

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

6.2.3 Compliance and Accountability

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

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.

6.2.4 Disposal and Destruction

After completion of the study, and following final drug inventory reconciliation by the site monitor, the study site will destroy or return all unused study drug supplies.

6.3 Patient Numbering and Treatment Assignment

6.3.1 Patient Numbering

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. Patient will be assigned in chronological order starting with the lowest number. Once a patient

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

6.3.2 Treatment Blinding

This is an open-label study.

6.4 Dosage and Administration

6.4.1 Zanubrutinib

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase. The investigator is to instruct the patient to take the study drug exactly as prescribed. Patients will be requested to bring their unused medication, including empty bottles, to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, approximately 12 hours apart, ± 2 hour time window. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

On days where both study drugs are administered, zanubrutinib will be given first and 30 minutes later the infusion of rituximab will be initiated.

[redacted]

The investigator or his/her designee must instruct the patient not to self-administer the study drug prior to the office visit on those days.

6.4.2 Rituximab

Rituximab will be administered at 375 mg/m^2 on Cycle 1 Days 1, 8, 15, 22, and on Day 1 of Cycles 4, 6, 8, 10.

For the infusion rate, please refer institutional standard. For additional information, please refer to the drug label.

Rituximab can cause severe, fatal infusion reactions. Patients should be pre-medicated with an

antihistamine and acetaminophen prior to each rituximab dosing. Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions is provided as needed. Depending on the severity of the infusion reaction and the required interventions, rituximab should be temporarily discontinued in the event of an infusion reaction. Infusion can be resumed at a minimum 50% reduction in rate after symptoms have resolved.

6.5 Dose Interruption and Modification

The guidelines set forth in Table 1 should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.5.1) or nonhematologic (Section 6.5.2) toxicities.

Table 1. Zanubrutinib Dose Reduction Levels for toxicity

Dose Level	Zanubrutinib Dose
0 (starting dose)	160 mg twice daily
-1	80 mg twice daily
-2	80 mg once daily

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

6.5.1 Zanubrutinib Dose Reductions for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting > 10 days, however earlier interruption is acceptable if medically indicated)
- Grade 4 thrombocytopenia (lasting > 10 days, however earlier interruption is acceptable if medically indicated)
- ≥ Grade 3 thrombocytopenia associated with bleeding
- ≥ Grade 3 febrile neutropenia

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. If the same event reoccurs, patients will restart at 1 dose level

lower upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions will be allowed. Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention will be discontinued from study treatment.

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

6.5.2 Zanubrutinib Dose Reductions for Nonhematologic Toxicity

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

6.5.3 Dose Modifications for Rituximab

No dose reductions for rituximab are allowed. A 28-day cycle length should be maintained, if possible. A rituximab dose delay of up to 5 days is acceptable from cycle 4.

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

6.6 Concomitant Medications and Non-Drug Therapies

6.6.1 Prior Therapy

The inclusion criteria (Section 5.1) specifies that patients should have received prior systemic therapy.

6.6.2 Concomitant Therapy

All concomitant medications, taken from 28 days prior to first dose of zanubrutinib, will be recorded in the eCRF with indication, dose information and dates of administration.

6.6.2.1 Permitted Medications

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

Bisphosphonate use is permitted if the patient has already been taken it for 3 or more months and on a stable dose.

Corticosteroid courses of limited duration (2 weeks or less) and dose (<20 mg prednisone per day, or equivalent) are permitted, if used to treat a concomitant (non-cancer) medical condition, with the exception of glucocorticoids used for management of rituximab-related infusion reaction.

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

6.6.2.2 Prohibited Medications

Patients should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement) while on treatment in this study.

Other anticancer therapy should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs

which requires permanent discontinuation of the study drug.

Chinese patent medicine for treatment of cancer are not allowed on study. Chinese herbal medications in the use of anticancer treatment is prohibited.

Live vaccines are prohibited during Screening and while on study treatment.

6.6.3 Potential Interactions Between the Study Drugs and Concomitant Medications

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 5 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and should consider using alternative agents. If these agents are used, follow the dose modification table in Table 2. The medical monitor should be consulted in these situations. Please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers 2019 for a more complete list.

Clinical drug-drug interaction study (BGB-3111-104) (refer to BGB-3111 Investigator's Brochure) indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Since blood levels and effectiveness of drugs that are substrates for CYP3A (eg, steroidal contraceptives) may be reduced by CYP3A inducers, if patients are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) is recommended to be used. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

Table 2. Dose Modification Table for Zanubrutinib When Co-Administered With Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

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

6.6.4 Surgery and Procedures

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

6.7 End of Treatment

All patients, regardless of reason for discontinuation of study treatment, will undergo an End of Treatment (EOT) visit within 7 days of discontinuing study drug. The reason for discontinuation from treatment will be recorded on eCRF. If a patient underwent study drug interruption > 7 days, before decision of permanent treatment discontinuation, an EOT visit can be done within the interval of 30 ± 3 days after the last dose of study drug, combining assessments at both EOT and Safety Follow-up visits.

Permanent treatment discontinuation is defined as cessation of study drug administration. Safety follow-up will be performed per Section 6.8.1.

The primary reasons that require patients to permanently discontinue study treatment are as follows:

- AE or intercurrent illness: Any intolerable AE that cannot be ameliorated by use of adequate medical intervention or that, in the opinion of the investigator or medical monitor, would lead to undue risk if study treatment were continued.
- Gross noncompliance with protocol: The medical monitor or investigator may request permanent discontinuation of study drug treatment in the event of a major protocol deviation, lack of cooperation, or noncompliance.
- Development of disease progression confirmed by investigator and medical monitor
- Need for long-term administration of prohibited concomitant therapy
- Death
- Loss to follow-up
- Sponsor discontinuation of study: The Sponsor reserves the right to terminate the study anytime as described in Section 6.9. The Sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.
- Patient decision: Patients may permanently discontinue study treatment anytime for any reason. Following study drug discontinuation, patients should have protocol required safety follow-up assessments 30 ±3 days after the last dose of study drug or immediately before commencing new anti-cancer treatment, which occurs first, unless the patient specifically declines further follow-up.

6.8 Follow-up Phase

6.8.1 Safety Follow-up

All patients who discontinue study treatment will have a Safety Follow-up Visit 30 days (±3 days) after the last dose of study drug (zanubrutinib or rituximab, whichever occurs later); or prior to the start of new anticancer therapy, whichever occurs first. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient has an ongoing laboratory abnormality at the

previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information.

6.8.2 Efficacy Follow-up

Disease status for patients who discontinue from study drug for reason(s) other than progressive disease (eg, AE) will be assessed radiographically by the same imaging modality as the Treatment Period. Tumor imaging will be performed every 12 weeks (± 7 days) since Cycle 1 Day 1, until progressive disease, withdrawal of consent, death, lost to follow-up, or End of Study, whichever occurs first.

6.8.3 Survival Follow-up

Following completion of the Safety follow-up phase, every effort should be made to follow patients via phone contact (with patient's guardian, if applicable) for survival approximately once every 3 months until patient death or study termination by the Sponsor. The investigator or his/her designee will also continue to collect information on new anti-cancer therapy given after the last dose of study drug until data cutoff for final analysis.

6.9 End of Study

For patients who continue to benefit from zanubrutinib treatment at the time of study closure, single agent zanubrutinib at the most recent tolerated dose may be continued after 2 years on study.

Premature discontinuation from the study (including all follow-up visits) will occur under the following circumstances:

- Patient withdrew consent
- Death
- Other

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

6.10 Loss to Follow-up

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

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

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

7 STUDY ASSESSMENTS

7.1 Study Procedures

7.1.1 Screening

A signed written informed consent form must be obtained from the patient prior to any study-specific procedures or assessments. Rescreening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the screening window (Day -28 to Day -1).

Procedures and assessments to be performed during the Screening window (Day -28 to Day -1):

- Informed consent
- Demographic
- Medical history and disease history including date of NHL diagnosis; date of last recurrence; prior treatments for NHL including chemotherapy, radiotherapy; dates of prior NHL treatments; stage of disease; International Prognostic Index (IPI) score at screening (One point each is allocated for age> 60years, stage III/IV disease, increased lactate dehydrogenase (LDH), ECOG performance status $\geq$2, $\geq$2 extra-nodal site involvement); and previous Epstein–Barr virus (EBV)-encoded RNA (EBER) result (if available)
- Inclusion/Exclusion Criteria
- Concomitant medications within 28 days prior to first dose of zanubrutinib
- CT with contrast and PET/CT of neck, chest, abdomen, and pelvis. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered. Total body MRI is allowed if contraindicated to CT with contrast. If scans were conducted within 30 days of the first dose of study treatment, then those scans are acceptable for screening.

- PET scan for patients with non-GCB DLBCL in cohort 1 while only patients with FL in cohort 2. If scan was conducted within 30 days of the first dose of study treatment, then that scan is acceptable for screening.
- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate
- Physical examination
- Adverse events
- 12-lead ECG
- Echocardiogram (ECHO) or multigated acquisition scan (MUGA), if not performed within 90 days of first day of Screening
- Complete blood count (CBC) with differential
- Comprehensive serum chemistry panel (Refer to Section 7.3.6.2)
- HBsAg, hepatitis B surface antibody (HBsAb), HBcAb, hepatitis C virus antibody (HCVAb), further testing by polymerase chain reaction (PCR) to assess HBV DNA level may be performed for determination of study eligibility as per the Inclusion/Exclusion Criteria.
- Coagulation parameters (prothrombin time [PT], aPTT, international normalized ratio [INR])
- Urinalysis
- HIV
- Serum pregnancy test (only in women of childbearing potential)
- Archival tumor tissue and/or a fresh tumor biopsy (10 to 15 unstained FFPE slides) to meet the requirement of biomarker analysis.
- Bone marrow aspirate and biopsy (immunohistochemistry [IHC]), if not performed within 60 days of first dose of study drug

Refer to the Schedule of Assessments (Appendix 2) for additional details.

The following eCRFs must be completed for screen-fail patients:

- Screening Phase Disposition page (include the reason for not starting treatment)
- Informed consent

- Demographics
- Serious adverse events
- Inclusion/Exclusion criteria

7.1.2 Cycle 1 Day 1 (minus 3-day window)

Procedures and assessments to be performed on Day 1 of Cycle 1 are listed below. A minus 3-day window is allowed for these assessments except where indicated.

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate
- ECG
- Height and weight
- Physical examination
- Adverse events
- Concomitant medications
- CBC with differential
- Comprehensive serum chemistry panel (Refer to Section 7.3.6.2)
- Urinalysis (In case where screening lab assessment for eligibility is completed within 72 hours of study drug administration, the urinalysis does not need to be performed again for C1D1.)
- Study drug administration (Cycle 1 Day 1 only)
- [redacted]

Refer to the Schedule of Assessments (Appendix 2) for further details.

7.1.3 Day 1 of Cycle 2 and All Subsequent Cycles (± 3-day window)

Procedures and assessments to be performed on Day 1 of Cycle 2 and all subsequent cycles include:

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate
- Weight

- Physical examination
- Adverse events
- Concomitant medications
- CBC with differential
- Comprehensive serum chemistry panel (Refer to Section 7.3.6.2)
- Urinalysis
- Study drug administration
- [redacted]

Refer to the Schedule of Assessments (Appendix 2) for further details.

7.1.4 End of Treatment

Procedures and assessments to be performed within 7 days after last dose of study drug, (If patient underwent study drug interruption > 7 days, before the decision of permanent treatment discontinuation, the EOT visit can be done within the interval of 30 ± 3 days after the last dose of study drug, combining assessments at both EOT and safety Follow-up visits):

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate
- Weight
- Physical examination
- Adverse events
- Concomitant medications
- CBC with differential
- Comprehensive serum chemistry panel (Refer to Section 7.3.6.2)
- Urinalysis
- CT with contrast of neck, chest, abdomen, and pelvis for confirmation of progressive disease, if progressive disease is the reason for discontinuation of treatment. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered. Tumor imaging for EOT does not have to be

performed if the most recent tumor imaging was performed within the previous 6 weeks.

- Serum pregnancy test
- PET scan for confirmation of progressive disease, if progressive disease is reason for discontinuation of treatment, for patients with non-GCB DLBCL in cohort 1 while only patients with FL in cohort 2.
- Core or excisional tumor biopsy, if an accessible lesion is present, or a 10 mL blood collection for patients who discontinued treatment due to progressive disease.

Refer to the Schedule of Assessments (Appendix 2) for further details.

7.1.5 Safety Follow-up

Procedures and assessments to be performed at the Safety Follow-up Visit (30 ± 3 days after last dose of study drug (zanubrutinib or rituximab, whichever occurs later) or immediately before commencing new anti-cancer treatment, whichever occurs first):

- Vital signs including temperature, blood pressure, pulse, respiratory rate
- Physical examination
- ECOG performance status
- 12-lead ECG
- Adverse events
- Concomitant medications
- CBC with differential
- Comprehensive serum chemistry panel (Refer to Section 7.3.6.2)
- Urinalysis

Refer to the Schedule of Assessments (Appendix 2) for further details.

7.1.6 Survival Follow-up

Following completion of the Treatment and Safety Follow-up phases of the study, every effort should be made to contact patients approximately every 3 months for anti-tumor treatment after EOT and survival status.

7.2 Efficacy Assessments

7.2.1 Imaging Studies

7.2.1.1 CT With Contrast

Tumor assessment by CT with contrast of neck, chest, abdomen, and pelvis will be performed at protocol specified time points (Refer to Appendix 2). Total body MRI is allowed if CT with contrast is contraindicated. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered.

CT scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In the case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed per the original plan schedule from baseline.

Response assessment for ORR will be by CT scan and categorized as per the Lugano Classification (Appendix 3).

7.2.1.2 PET

Tumor assessment by PET will be performed at Screening, Week 24, Week 48, and at CR or progressive disease suspected clinically or radiographically (Refer to Appendix 2) for sites with PET scanning capability for patients with non-GCB DLBCL and FL until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.

Response assessment for ORR will be by PET scan and categorized as per the Lugano Classification (Appendix 3).

7.2.2 Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy will be required at Screening, if not performed within 60 days of first dose of study drug. Repeat bone marrow aspirate and biopsy are required at the time of CR for confirmation of response if baseline marrow examination is positive for NHL involvement.

7.2.3 Archival or Fresh Tumor Collection

Archival or a fresh tumor sample (paraffin embedded block or 10-15 unstained FFPE slides) will be collected at Screening to meet the requirement of biomarker detection. Additionally, an optional

tumor biopsy will be obtained at EOT for accessible tumor if reason for treatment discontinuation is progressive disease. An optional tumor biopsy will also be collected for accessible tumor from patients who fail to achieve PR or better after at least 6 months of study treatment. See Section 7.4.1 for more information.

7.3 Safety and Tolerability Assessments

Safety assessments should be performed at all visits by the investigator throughout the study. Safety assessments will consist of monitoring all AEs and SAEs, regular monitoring of blood tests, urine tests, vital signs, weight, performance status, and physical examinations. For schedule of study visits, refer to the Schedule of Assessments (Appendix 2).

7.3.1 Adverse Events

Record adverse events that occurred during screening both in the medical history case report form and the patient's clinical record.

Collect nonserious AE information from the time of first dose of study drug. Information on all SAEs (regardless of relatedness) will be collected from the time of signed informed consent. The AE reporting period is defined in Section 9.4.

All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 9.1.1. Important additional requirements for reporting SAEs are explained in Section 9.

7.3.2 Physical Examination, Vital Signs, Height, and Weight

Physical examination, vital signs (sitting blood pressure, heart rate, respiratory rate, body temperature), and weight will be performed at each study visit. Height (cm) is determined at screening only.

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

Assessment of vital signs and a focused physical examination on the first day of cycle 1 may be skipped if performed within 7 prior days. Physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen,

back, lymph nodes, extremities, and a basic nervous system evaluation. A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), and weight will be performed at each study visit. To the extent feasible, blood pressure will be taken on the same arm throughout the study. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is > 150/100 mmHg in a patient without a history of hypertension, or increased by > 20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Weight will be measured on Day 1 of each treatment cycle.

7.3.3 Medical and Cancer History

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

Other background information including history of disease, including the date of initial diagnosis and current disease status, staging, and sites of disease (see Appendix 4). Prior medications/significant non-drug therapies and demographic data (gender, date of birth [or age] and race/ethnicity) will also be collected. The investigator will obtain the patient's medical history at the Screening visit. Medical history will include all active conditions, and any conditions diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Significant findings that were present prior to the signing of the informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF.

7.3.4 ECOG Performance Status

ECOG performance status (Table 3) will be assessed at the Screening Visit, Day 1 of each treatment

cycle, End of Treatment Visit, and at the Safety Follow-up Visit.

Table 3. ECOG Performance Status

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

Abbreviation: ECOG, Eastern Cooperative Oncology Group

7.3.5 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed in triplicate at screening. Patients should be in the semi-recumbent or supine position. The Cycle 1 and Safety Follow-up ECGs should be performed pre-dose.

7.3.6 Laboratory Evaluations

Screening blood tests performed within 3 days of the first study drug administration do not need to be repeated on Cycle 1 Day 1. Abnormal laboratory values will constitute AEs only if they are associated with clinical signs or symptoms that are clinically significant and/or require therapy, and should be recorded on the AEs eCRF. In addition, isolated abnormal laboratory values that are considered clinically significant (eg, cause study discontinuation or constitutes in and of itself an SAE) should be recorded on the AEs eCRF.

7.3.6.1 Hematology

CBC with differential is required to be performed every visit during the treatment phase. CBC includes hemoglobin, hematocrit, reticulocyte, platelet count, red blood cell count, white blood cell count with differential including neutrophils (including bands), lymphocytes, monocytes,

eosinophils, and basophils. In the event of neutropenia or thrombocytopenia, these assessments will be conducted as frequently as the investigator feels it necessary until toxicity resolves to ≤ Grade 2.

7.3.6.2 Clinical Chemistry and Immunoglobulins

Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or urea), creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, LDH, and alkaline phosphatase. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels it necessary until toxicity resolves to ≤ Grade 2. Total immunoglobulins will be obtained every 6 months, including IgG, IgM, IgA.

7.3.6.3 Coagulation

Coagulation studies including PT, INR, and aPTT will be performed at Screening. Repeat testing may also be performed as clinically indicated during the Treatment Period including for those patients on anticoagulation therapy as approved by the medical monitor.

7.3.6.4 Urinalysis

Urinalysis will be performed at screening, and at every visit during the treatment period and EOT, using a urine dipstick. Urine microscopy will be performed if the urine dipstick is abnormal. The assessment includes: pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If the urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and creatinine will be obtained and evaluated.

7.3.6.5 Hepatitis B and Hepatitis C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as HBV DNA by PCR if the patient is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or HBV DNA ≥ 500 IU/mL or detectable level of HCV RNA (≥ 15 IU/mL) are not eligible. Patients who are HBsAg negative and HBcAb positive must initiate the anti-viral therapy before the first dose of study treatment and undergo monthly HBV DNA screening by PCR. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B and the medical monitor.

Patients positive for HCV antibody but negative for HCV RNA (<15 IU/mL) must undergo monthly HCV RNA screening. Patients with known HIV are excluded from the study. Patients with detected HCV RNA should stop study drug and anti-viral therapy should be initiated. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 4 below, shows how the results for HBV, and HBV testing at screening relate to Inclusion and Exclusion criteria.

Table 4. Active Hepatitis B or HCV Infection (Detected Positive by Polymerase Chain Reaction)

Screening Assessment	**Meets Inclusion Criteria**	**To be Excluded**
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA < 500 IU/mL* *and* *anti-viral therapy is started prior to first dose of study treatment and throughout the study treatment* *and* *Perform monthly monitoring of HBV DNA*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA ≥ 500 IU/mL*[1]
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not-detected" (<15 IU/mL)* *Perform monthly monitoring of HCV RNA*	**Antibody (+)** *HCV RNA Detected*[1]

Abbreviation: IU, International unit; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus
Note: Please refer to Section 7.3.6.5 above.

7.3.6.6 Pregnancy Test

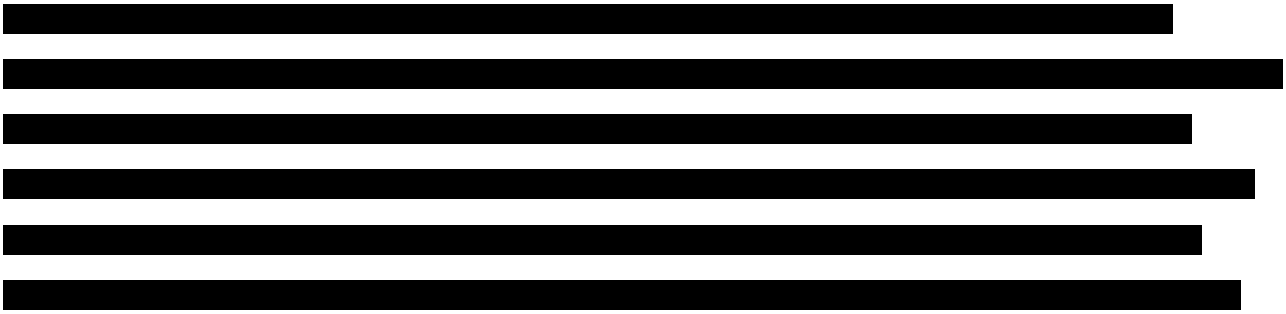
A serum pregnancy test will be performed at Screening and EOT for women of childbearing potential. Any female patient who is pregnant will not be eligible for the study. Patients must have a negative serum pregnancy test at Screening. Subsequent tests may be urine tests, and should be performed as clinically indicated. A patient who has a positive pregnancy test result at any time after initiation of study treatment will be immediately withdrawn from participation in the study.

7.4 Other Assessments

7.4.1 Biomarker Analysis

Patients who have DLBCL must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype and further genetic analysis. Either a FFPE block with tumor tissue (preferred) or 10 to 15 unstained slides must be sent to the central laboratory (to meet the requirement of biomarker analysis) to conduct exploratory biomarker analysis such as DNA panel sequencing, IHC and gene expression profile (GEP) to confirm the DLBCL subtype. Other biomarkers will also be assessed, including but not limited to EBV status, myelocytomatosis (MYC)/B-cell lymphoma (BCL) 2/BCL6 rearrangement and expression, etc. Pathology and IPI information will be collected from the site, if available.

Patients who have FL and MZL must have archival tumor tissues or agree to a tumor biopsy for biomarker genetic analysis such as DNA panel sequencing. Either a FFPE block with tumor tissue (preferred) or 10 to 15 unstained slides must be sent to the central laboratory (to meet the requirement of biomarker analysis).



Please refer to Lab Manual for more details.

8 DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the contract research organization's (CRO's) qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

8.1 Data Collection

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.

8.2 Data Management/Coding

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

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

During the course of the study, a study monitor (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

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 Definitions and Reporting

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

Examples of an AE include:

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

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation

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

9.1.1.1 Assessment of Severity

The investigator will assess the intensity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE Version 4.03). 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 [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets one of the pre-defined outcomes 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 his/her clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapies, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated. The investigator will also consult the IB, 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/eCRF accordingly.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions:

• Related: There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (When necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment.
• Probably related: This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study treatment that: There is reasonable temporal relationship; the occurrence of AE could not be explained by the patient's medical history, concurrent medical condition, or other the patient's signs or symptoms; the positive of de-challenge result; the positive of re-challenge result.

• Possibly related: 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, other concomitant AEs).

• Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the AE.

• Not rrelated: An AE will be considered "not related" to the use of the product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (eg, the AE occurred either before, or too long after administration of the product for it to be considered product-related);
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

The causality for cases assessed with 5-point scale will be mapped to 2-point scale during aggregate safety data analysis according to the BeiGene latest mapping rule.

9.1.1.3 Follow-Up of Adverse Events and Serious Adverse Events

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

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

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

The Sponsor or designee may request that the investigator performs or arranges 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/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be re-sent to the Sponsor or designee within the time frames outlined in Section 9.7.

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 AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worse will not be reported as AEs or SAEs. The definition of clinically significant is left to the judgment of the investigator; in general, these are events that result in clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation.

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

9.1.3 Lack of Efficacy

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

9.2 Serious Adverse Events

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 was 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 outpatient 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.

- Results in disability/incapacity.

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

- Is a congenital anomaly/birth defect

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

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline

- Hospitalization for social/convenience considerations

- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug event, the specificity

or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure. This refers to any AE that has not been previously observed (eg, included in the Investigator's Brochure), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

9.4 Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.4.1 Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of zanubrutinib or 90 days after the last dose of rituximab, whichever is longer. Patients with an ongoing AE that leads to treatment discontinuation will be followed until either the event resolves, the investigator assesses the event as stable, or the patient is lost to follow-up. After this period, the investigator should report any AE/SAEs that are believed to be related to prior study drug treatment.

9.4.2 Eliciting Adverse Events

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

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

All AEs and SAEs will be recorded in the source documents and eCRFs.

9.5 Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.5.1 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.

9.5.2 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.

9.5.3 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 resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

9.5.4 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 or

brain metastasis. If a patient experiences multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on the 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.

9.5.5 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."

9.6 Recording of Adverse Events and Serious Adverse Events

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 or designee. In these instances, all patient identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor or designee. When a SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE form. It is not acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor or designee in lieu of completion of the appropriate SAE form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this instance, all patient identifiers will be redacted on the copies of the medical records prior to submission to the Sponsor or designee.

9.7 Prompt Reporting of Serious Adverse Events

9.7.1 Time Frame for Submission of Serious Adverse Events

Serious adverse events will be reported promptly to the Sponsor or designee within 24 hours once

the investigator determines that the event meets the protocol definition of a SAE (Table 5).

Table 5 Timeframe for Reporting Serious Adverse Events to the Sponsor or Designee

Type	Initial Report	Document	Follow-up SAE Report	Document
All SAEs	Within 24 hours of first knowledge of the AE	SAE form	As expeditiously as possible	Updated SAE form

9.7.2 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 or designee within 24 hours as outlined in Section 9.7.1. The SAE report form will always be completed as thoroughly as possible with all available details of the SAE, e-signed by the investigator (or designee) and forwarded to the Sponsor within the designated time frames. If the investigator does not have all the information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor of the event and will complete 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.

If the EDC system is nonoperational, facsimile transmission of the paper SAE form is the preferred backup method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by email is acceptable, with a copy of the paper SAE form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the paper SAE form within the time frames outlined in Section 9.7.1. After the EDC becomes operational again, the investigator will enter the information in the EDC system.

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

9.7.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the Sponsor or designee in accordance with the procedures detailed in Section 9.7.2. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

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

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 included in 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 Investigator's Brochure) from the Sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.8 Serious Adverse Events Related to Study Participation

A SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre-or post-treatment period, will be reported promptly to the Sponsor or designee (Section 9.7).

9.9 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, or a female patient pregnant while receiving

rituximab or within 12 months after the last dose of rituximab, a pregnancy report form should be completed and expeditiously submitted to the Sponsor or designee to follow up with the patient. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

A serum pregnancy test will be performed at Screening and EOT in women of childbearing potential. Any female patient who is pregnant will not be eligible for the study. A urine or serum pregnancy test must be performed if any woman suspects that she has become pregnant during the study.

9.9.1 Action to be Taken and Reporting if a Pregnancy Occurs

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 investigator or his/her designee will collect pregnancy information on any female patient or a female partner of a male patient who becomes pregnant while participating in this study. The investigator or his/her designee will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 2 weeks of learning of a patient's or male patient's female partner's pregnancy. The patient or male patient's female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or designee.

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, and will be followed.

A spontaneous abortion is always considered to be a SAE and will be reported as described

previously. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study drug by the investigator will be reported to the Sponsor or designee. While the investigator is not obligated to actively seek this information in former patients, he/she may learn of a SAE through spontaneous reporting.

9.10 Post-Study Adverse Events and Serious Adverse Events

A post-study AE or SAE is defined as any AE that occurs after the AE/SAE detection reporting period.

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

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

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

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

- BGB-3111 Investigator's Brochure
- Local prescribing information for rituximab

10 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

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

10.1 Sample Size

Total sample size for the study will be approximately 40 patients, 20 for each cohort. There will be no hypothesis testing for study endpoints, thus the sample size is not based on the statistical power calculation.

10.1.1 Analysis Sets

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

All patients for whom valid zanubrutinib PK can be estimated and no important protocol deviations affecting PK will be included in the PK Analysis Set on an as treated basis. Similarly, patients for whom valid rituximab PK can be estimated and no important protocol deviations affecting PK will be included in the PK Analysis Set on an as treated basis. For exploratory parameters, all patients for whom can be estimated on with evaluable data will be included in the summaries.

10.1.2 Interim Analysis

No interim analysis is planned for this study.

10.1.3 Withdrawal

Patients who withdraw from the study will not be replaced.

10.1.4 Pharmacokinetics

Plasma and serum samples for analysis of zanubrutinib and rituximab respectively will be collected at the time points described in Section 7.1 and Schedule of Assessments (Appendix 2).

Plasma zanubrutinib and serum rituximab concentrations will be summarized and displayed in tabular format.

Additional analyses such as population PK analysis may be performed in conjunction with data from other studies and the results from such analyses may be reported separately from the clinical study report (CSR).

10.2 Efficacy Data Analysis

Response assessment for disease status-based efficacy endpoints (ORR, CR, CMR, PFS, time to response [TTR] and DOR) will be performed per the Lugano Classification (Cheson et al 2014).

10.2.1 Primary Efficacy Endpoint

The primary endpoint of the study is ORR by investigator. ORR will be calculated as crude proportion of number of patients who achieve PR or higher as best response. The estimate of ORR with 95% exact confidence interval will be presented in each cohort.

10.2.2 Secondary Efficacy Endpoints

CR and CMR will be analyzed using the same methods applied for ORR analysis. Listings for time to event secondary efficacy endpoints (PFS, DOR, overall survival [OS] and TTR) will be generated. The distribution of time to event secondary efficacy endpoints will be estimated where applicable.

10.3 Safety Data Analysis

10.3.1 Adverse Event

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using the MedDRA®. AEs will be coded to the MedDRA® (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA® preferred term and primary system organ class are also captured in the database.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose date of study drug up to 30 days following discontinuation of zanubrutinib or 90 days following discontinuation of rituximab, whichever comes later; or initiation date of new anticancer therapy, if it occurs prior to the other two dates. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by

system organ class and preferred term. A patient will be counted only once by the highest severity grade according to the NCI-CTCAE Version 4.03 within a system organ class and preferred term, even if the patient experienced more than 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. The treatment-related AEs include those events considered by the investigator to be related, possibly or probably related, unlikely related to study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs ≥ Grade 3, related TEAEs, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

10.3.2 Laboratory Assessments

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

Laboratory parameters that are graded in NCI-CTCAE Version 4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

10.3.3 Electrocardiogram

All ECG parameters, including the QT interval corrected for heart rate (QTc), will be listed for each patient.

10.3.4 Vital Signs

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

10.3.5 Extent of Exposure

Extent of exposure to zanubrutinib in combination with rituximab will be calculated for each patient. Extent of exposure to study drug will be summarized descriptively as the number of cycles received, duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity (%), as appropriate.

The number (percentage) of patients with dose reductions, dose interruption, and drug discontinuation will be summarized with the respective reasons, as appropriate. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of dose reductions and interruptions will be summarized descriptively, as appropriate.

Patient data listings will be provided for all dosing records.

10.3.6 Physical Examination

Physical examination results will be listed.

10.3.7 Other Safety Endpoints

ECOG performance status will be summarized. Pregnancy test and viral serology will be listed.

10.4 Explorative Endpoint Analyses

[redacted]

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory Authority Approval

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

11.2 Investigator Responsibilities

11.2.1 Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the Declaration of Helsinki International Conference on Harmonization (ICH) guidelines, and that the basic GCP principles, 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.

Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before the participation of the investigator and any sub-investigator. The Investigator and sub-investigator(s) agree to notify BeiGene of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol defined activities.

11.2.2 Ethical Conduct of the Study and Ethics Approval

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

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

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The

investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before a new patient consents to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded immediately to the Sponsor.

11.2.3 Informed Consent

The investigator is responsible for obtaining written informed consent from all patients participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study is given and before performing any study-related procedures. The investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Before patient participation begins, each informed consent will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

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

11.2.4 Investigator Reporting Requirements

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 study conduct at the study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the Sponsor.

11.2.5 Confidentiality

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent form (ICF) process, either as part of the ICF or as a separate signed document (eg, in the US, a site-specific Health Insurance Portability and Accountability Act [HIPAA] consent may be used). The investigator must assure that the patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials (if 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, case report forms (CRFs), the investigational new drug, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.2.6 Case Report Forms

For each patient 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 exists within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the 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 for that site on CD-ROMs for archiving the data at the study site.

11.2.7 Drug Accountability

The investigator or designee (eg, 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 dispensing records and returned or destroyed study product. Dispensing records will show quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials (if allowed), 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 in order to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site, BeiGene or its representative to destroy or return of unused study drug supplies.

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

11.2.8 Inspections

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

11.2.9 Protocol Adherence

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

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

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

before changes can be implemented.

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

11.3.2 Study Report and Publications

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

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

11.4 Study and Study Center Closure

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

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

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

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

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

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

11.5 Records Retention and Study Files

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

clinical source documents.

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

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

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

11.6 Provision of Study Results and Information to Investigators

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

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

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

11.7 Information Disclosure and Inventions

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

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

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

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other

study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.
- Information which is necessary to disclose in order to provide appropriate medical care to a patient.
- Study results which may be published as described in Section 11.3.2.

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

11.8 Joint Investigator/Sponsor Responsibilities

11.8.1 Access to Information for Monitoring

In accordance with 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 during these monitoring visits are resolved.

11.8.2 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor or its designee immediately. The investigator agrees to

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

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13 APPENDICES

Appendix 1. Signature of Investigator

PROTOCOL TITLE: A Phase 2 Study to Assess the Safety, Tolerability, and Activity of BGB-3111 in Combination with Rituximab in Chinese Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)

PROTOCOL NO: BGB-3111-213

This protocol is a confidential communication of BeiGene (Beijing) Co., Ltd. I confirm that I have read this protocol, I understand it, and I will work in accordance with 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 (Beijing) Co., 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 the contract research organization (CRO).

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. Schedule of Assessments

	Screening [1]	Treatment Period			Safety Follow-up [2]	Survival/Efficacy Follow-up [3]
		Cycle 1	Cycle 2 and additional cycles (every 28 ± 3 days)	EOT [4]		
Days	**-28 to -1**	**1** [5]	**1** [5]		**30 ± 3 days after last dose of study drug**	
Informed consent [6]	x					
Inclusion/exclusion criteria	x					
Demographic/Medical history/ Disease staging/Prior medications/IPI score/EBV infection [7]	x					
Vital signs [8]	x	x	x	x	x	
Height and weight [9]	x	x	x	x	x	
Physical examination	x	x	x	x	x	
ECOG performance status	x	x	x	x	x	
12-lead ECG [10]	x	x			x	
Review adverse events [11]	x	x	x	x	x	
Review concomitant medications [12]	x	x	x	x	x	
CBC with differential [13]	x	x [5]	x [5]	x	x	
Serum chemistry panel [13]	x	x [5]	x [5]	x	x	
Coagulation parameters [14]	x					
Urinalysis [15]	x	x	x	x		
Immunoglobulins		x [16]	x [16]			
Hepatitis B and C [17]	x					

	Screening [1]	Treatment Period			Safety Follow-up [2]	Survival/Efficacy Follow-up [3]
		Cycle 1	Cycle 2 and additional cycles (every 28 ± 3 days)	EOT [4]		
Days	**-28 to -1**	**1 [5]**	**1 [5]**		**30 ± 3 days after last dose of study drug**	
HIV	x					
Pregnancy test [18]	x			x		
Tumor tissue collection for biomarker study [19]	x		When patient fails to achieve partial response (PR) or better after at least 6 months of study treatment	x		
Blood collection for biomarker study [20]	x		When patient fails to achieve partial response (PR) or better after at least 6 months of study treatment	x		
CT or PET/CT or MRI [21, 22]	x	Week 12, then every 12 weeks, ± 7 days		x [22]		x [22]
PET [23]	x	Week 24, Week 48, clinical CR or progressive disease suspected clinically or by CT (MRI if CT contraindicated)				x
ECHO or MUGA [24]	x					
Bone marrow aspirate/biopsy [25]	x	For confirmation of CR if baseline marrow is positive for NHL				
Survival status						x
Zanubrutinib administration		orally twice daily, continuously				
Rituximab administration		Days 1, 8, 15, 22 of Cycle 1, then Day 1 of Cycles 4, 6, 8, and 10				
[redacted]		[redacted]	[redacted]			

	Screening [1]	Treatment Period			Safety Follow-up [2]	Survival/Efficacy Follow-up [3]
		Cycle 1	Cycle 2 and additional cycles (every 28 ± 3 days)	EOT [4]		
[redacted]						

Abbreviation: CBC, complete blood count; CT, computed tomography; EBV, Epstein–Barr virus; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; IPI, International Prognostic Index; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PET, positron emission tomography.

[1] All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Screening procedures may be performed up to 28 days prior to first dose of treatment. If CT and PET scans were conducted within 30 days of the first dose of study treatment, then those scans are acceptable for screening.

[2] The mandatory Safety Follow-up Visit should be conducted 30 days (±3 days) after the last dose of study therapy (zanubrutinib or Rituximab, whichever is later) or before the initiation of a new treatment, whichever comes first.

[3] Following completion of the Safety follow-up phase, every effort should be made to follow patients for survival approximately once every 3 months until patient death or study termination by the Sponsor. For patients who discontinue study treatment for reason other than progressive disease, disease status should be captured every 12 weeks (± 7 days) until progressive disease, withdrawal of consent, death, lost to follow-up, end of study or study termination by Sponsor, whichever occurs first.

[4] When patients go off treatment, they will need to undergo EOT visit within 7 days of last dose of study drug. If patient underwent study drug interruption > 7 days, before decision of EOT, EOT visit can be done within the interval of 30 ± 3 days after last dose of study drug, combining assessments at both EOT and safety Follow-up visits.

[5] In Cycle 1, tests may be performed 3 days prior to Day 1 of the cycle. In Cycle 2 and beyond, tests may be performed within a 3-day window of Day 1 of the cycle.

[6] Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe (eg, within 28 days prior to Cycle 1 Day 1). Assign baseline number when the study informed consent is signed.

[7] Includes history for the primary diagnosis (date of NHL diagnosis and last recurrence, stage, and biopsy details), treatment of NHL including prior systemic,

radiation treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 28 days prior to the Screening visit (Visit 1). Disease staging should be recorded as per criteria in Appendix 4. Collect IPI score at screening (One point each is allocated for age>60years, stage III/IV disease, increased LDH, ECOG performance status >2, >2 extra-nodal site involvement) and previous EBER result (if available).

[8] Vital signs to include temperature, blood pressure, pulse, respiratory rate.

[9] Height (cm) is determined at Screening only.

[10] At each time point listed, triplicated 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes. Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the patient's medical chart and the second copy will be kept in the study file for retrospective collection by the Sponsor if necessary.

[11] Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE version 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. AE and SAE will be reported until 30 days after the last dose of zanubrutinib, or 90 days after the last dose of rituximab, whichever occurs later. See Section 9 for details regarding the reporting of AEs.

[12] All Concomitant Medications within 28 days prior to first study treatment and until 30 days after the last dose of study treatment should be recorded in the CRFs. Any new anti-cancer therapy, if taken after treatment discontinuation, will also be recorded.

[13] If screening lab assessment for eligibility is completed within 3 days of study drug administration, they do not need to be performed again for C1D1. Re-screening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the Screening window (Day -28 to Day -1). In Cycle 2 and beyond, laboratory assessments can be done within 48 hours of the visit and do not necessarily need to be on the day of the visit.

[14] Coagulation parameters (PT, INR, aPTT) should be determined at Screening and during study treatment as clinically indicated.

[15] Urinalysis will be performed at screening, every visit during the treatment period and EOT. In case where screening lab assessment for eligibility is completed within 72 hours of study drug administration, the urinalysis does not need to be performed again for C1D1. The testing includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If urine protein is ⩾2+ by dipstick, a 24-hour urine for total protein and creatinine will be obtained and evaluated.

[16] Total immunoglobulins will be obtained every 6 months, including IgG, IgM, IgA.

[17] Testing will be performed at Screening and includes Hepatitis C virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb). Patients who are HBcAb positive at Screening must not be enrolled until further testing by PCR to assess Hepatitis B viral load for determination of study eligibility as per Inclusion/Exclusion Criteria (See Section 5.2 and Section 7.3.6.5).

[18] Serum pregnancy test (only in women of childbearing potential) at screening and at EOT. Patients must have a negative serum pregnancy test at Screening. Subsequent tests may be urine tests and should be performed as clinically indicated.

[19] Archival or newly obtained tumor tissue from a core or excisional biopsy will be collected (paraffin block or 10-15 unstained FFPE slides) to meet the requirement of biomarker analysis at Screening. Optional tumor biopsy will be obtained at EOT for accessible tumor if reason for treatment discontinuation is progressive disease. Optional tumor biopsy will also be collected for accessible tumor from patients who fail to achieve partial response (PR) or better after at least 6 months of study treatment.

[20] Blood samples (10 ml) will be collected at screening. In addition, blood samples will be collected from patients who fail to achieve partial response (PR) or better after at least 6 months of study treatment. Another 10 ml blood sample will be obtained at EOT if the reason for treatment discontinuation is progressive disease.

[21] Tumor imaging (CT with contrast of neck, chest, abdomen and pelvis, and PET/CT) will be performed within 28 days prior to the first dose of study drug

treatment. Any qualified imaging assessments already completed during the regular work-up of the patient are accepted within 28 days prior to start of treatment, including before signing the main study informed consent form, and can be considered as the Screening/baseline image for this study. Imaging timing should follow calendar days and should not be adjusted for treatment delays. Tumor assessments by CT with contrast should be performed at Screening, Week 12, then every 12 weeks (± 7 days) until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever is earlier. Target and non-target lesions must be identified at the time of Screening and the same lesion(s) must be re-assessed by investigator at each time point in a consistent manner in accordance with the Lugano Classification (Cheson et al 2014). The same diagnostic modality must be used throughout the study. PET/CT can be performed in lieu of a CT with contrast only if the CT is performed with diagnostic quality and contrast is administered. Total body MRI may be substituted for CT if CT with contrast is contraindicated.

22 Tumor imaging for EOT does not have to be performed if the most recent tumor imaging was performed within the previous 6 weeks. For patients who discontinue study treatment for reason other than progressive disease, tumor imaging will be performed every 12 weeks (± 7 days) until progressive disease, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.

23 Tumor assessment by PET scan will be performed at Screening, Week 24, Week 48, progressive disease suspected clinically or by CT (MRI if CT contraindicated), and CR suspected clinically or by CT (MRI if CT contraindicated), for sites with PET scanning capability. For patients with diagnosis of MZL, PET scan is not required at Screening or on study treatment.

24 ECHO or MUGA is required at Screening unless performed within 90 days of first day of Screening (Visit 1).

25 Bone marrow aspirate and biopsy will be performed at Screening, if not performed within 60 days of first dose of study drug. Bone marrow aspirate and biopsy will also be required for confirmation of CR if baseline marrow was positive by NHL.

26 [redacted].

Appendix 3. The Lugano Classification for Response Assessment

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Response	Complete metabolic response	Complete radiologic response (all of the following): 1. Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi 2. No extra-lymphatic sites of disease
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	
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, IHC negative
Partial Response	Partial metabolic response	Partial remission (all of the following): • ≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal 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

Response and Site	PET-CT-Based Response	CT-Based Response
Lymph nodes and extra-lymphatic 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	
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
No response or stable disease	No metabolic response	Stable disease < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5[+] with no significant change in FDG uptake from baseline at interim or end of treatment	
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression

Response and Site	PET-CT-Based Response	CT-Based Response
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 PPD progression:
		An individual node/lesion must be abnormal with:
		• LDi > 1.5 cm and
		• Increase by ≥ 50% from PPD nadir and
		• An increase in LDi or SDi from nadir
		  o 0.5 cm for lesions ≤ 2 cm
		  o 1.0 cm for lesions > 2 cm
		• In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
		• New or recurrent splenomegaly

Individual target nodes/nodal masses	Score 4 or 5[+] with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	
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 (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Source: Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-67.

Abbreviation: CT, computed tomography; FDG, fluorodeoxygluose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; PPD, cross product of the longest transverse diameter of a lesion and perpendicular diameter; SDi, shortest axis perpendicular to the longest transverse diameter of a lesion; SPD, sum of the product of the perpendicular diameters for multiple lesions; 5PS, 5-point scale.

*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 extra-nodal 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), GI 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 extra-nodal 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 extra-nodal sites (eg, GI 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).

†Splenomegaly defined as vertical spleen length > 13 cm for purposes of the CT reads.

†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

Appendix 4. Non-Hodgkin Lymphoma Staging

Stage	Involvement	Extra-nodal (E) Status
I	One node or a group of adjacent nodes	Single extra-nodal lesion without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with bulky disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional non-contiguous extra-lymphatic involvement	Not applicable

Source: Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-67.

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Bulky disease defined as a single nodal mass of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined radiographically.

Appendix 5. CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
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

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers.

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

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol. For a more complete list, please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers List (FDA 2019).