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CLINICAL STUDY PROTOCOL TITLE PAGE

A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib in Patients With CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Brief Title:

A Study of Zanubrutinib in Patients With CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Protocol Number:	BGB-3111-218
Amendment Number:	Amendment 3.0
Investigational Medicinal Product:	Zanubrutinib (BGB-3111)
Regulatory Agency Identification Number(s):	Not applicable
Sponsor:	BeiGene (Suzhou) Co., Ltd. Building 9, Biological Industrial Park No. 218 Sangtian Street, Suzhou Industrial Park China (Jiangsu) Pilot Free Trade Zone Suzhou Area
Approval Date:	*See electronic signature*
Contact Information:	BeiGene Medical Officer Phone: 1.877.828.5568 Email: clinicaltrials@beigene.com

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INVESTIGATOR SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to study BGB-3111-218 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated. This includes personnel at my site as well as personnel working in any facility where study activities are my responsibility.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable laws and regulations, the requirements of the ethics committee of record for my clinical site, and current GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients before initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site before initiating any study-specific procedures or administering investigational products to those patients.
- To maintain records of each patient's participation and all data required by the protocol in an accurate and timely manner.

Acceptance of this protocol constitutes my agreement that no confidential information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd. or one of its affiliates, unless and only to the extent required by applicable laws and regulations.

Name: *Last name, First name*	**Title:** *Title at Institution*	**Institution:** *Address*
Signature:		**Date:** *DD Month YYYY*

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DOCUMENT HISTORY

Amendment Version Number	Approval Date	Type of Protocol Amendment
BGB-3111-218 Amendment 2.0	07 September 2022	Non-substantial
BGB-3111-218 Amendment 1.0	15 February 2022	Substantial
Original protocol	18 November 2020	Not applicable

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

This Protocol Amendment 3.0 replaces the previous Protocol Amendment 2.0. The primary purpose of Amendment 3.0 is to:

- Remove IRC-dependent assessments;
- Remove CDx development;
- Clarify that there would be options for patients to continue treatment after study closeout;
- Update data of zanubrutinib and contraception language to align with the current investigator's brochure.

The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 2 Study Objectives Section 3.1 Summary of Study Design Section 3.2 Figure 1 Study Schema Section 5.7 Efficacy Assessments Section 5.7.1 Radiographic Imaging Section 5.14 Long-Term Follow-up Section 9.1 Study Endpoints Section 9.1.2 Secondary Endpoints Section 9.2.5.2 Secondary Efficacy Endpoint Analyses Section 10.2 Independent Review Committee (deleted section) Appendix 1 Schedule of Assessments Footnotes c, s, t	Removed IRC-dependent assessments and the definition of IRC.	To convert the study from a potential pivotal study to a proof-of-concept study.
Section 5.4.1 Prescreening Section 5.10 Biomarker Assessments Appendix 1 Schedule of Assessments Footnote h	Removed CDx development and updated to allow residual samples for exploratory biomarker testing.	To convert the study from a potential pivotal study to a proof-of-concept study.
Section 5.15 End of Study	Updated the language to state that patients who may benefit from zanubrutinib could be offered the option to continue treatment after the end of the study.	To clarify that there would be options for patients to continue treatment after study closeout.
Section 3.1 Summary of Study Design Section 5.7.1 Radiographic Imaging	MRI **and a non-contrast chest CT scan** may be used instead of contrast CT for patients with serious contrast allergy.	For clarity and feasibility.

Section Number and Title	Summary of Change	Brief Rationale for Change
Appendix 1 Schedule of Assessments Footnote t		
Section 4.1 Inclusion Criteria Section 5.3 Females of Childbearing Potential and Contraception Section 5.8.6 Pregnancy Test Section 8.7 Pregnancy Reporting Appendix 1 Schedule of Assessments Footnote aa	Updated the requirements for contraception and pregnancy testing/reporting to align with the current investigator's brochure.	For consistency.
Section 1.4 Background Information on Zanubrutinib (BGB-3111) Section 1.4.1 Nonclinical Data for Zanubrutinib Section 1.4.3.3 Phase 2 Study BGB-3111-213 Section 1.6 Benefit-Risk Assessment	Updated to align with the current investigator's brochure.	To provide the most current data of zanubrutinib.
Section 8.1.1.3 Following Adverse Events and Serious Adverse Events Section 8.4.1 Adverse Event Reporting Period Appendix 1 Schedule of Assessments Footnote r	Added the endpoint of **initiation of any alternative anticancer therapy** for initial/follow-up reporting period of all AEs and SAEs.	For clarity and consistency throughout this protocol.
Clinical Study Protocol Title Page, Investigator Signature Page Appendix 6 Signature of Investigator (deleted appendix)	Updated the current study information per the current guidance and template.	To update for administrative purposes and consistency with the protocol template.
Document History	Added Document History page.	For consistency with the protocol template.

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SYNOPSIS

Name of Sponsor/Company: BeiGene (Suzhou) Co., Ltd.
Investigational Product: Zanubrutinib (BGB-3111)
Title of Study: A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib in Patients With CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma
Protocol Identifier: BGB-3111-218
Phase of Development: 2
Number of Patients: Approximately 66 patients will be enrolled.
Objectives of Study **Primary Objective** • To evaluate the efficacy of zanubrutinib in patients with CD79B mutant relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), as measured by overall response rate determined by the investigator assessment in accordance with the 2014 modification of the International Working Group on non-Hodgkin lymphoma (NHL) Criteria (hereafter referred to as the Lugano classification) (Cheson et al 2014). **Secondary Objectives** • To evaluate the efficacy of zanubrutinib in patients with CD79B mutant R/R DLBCL, as measured by the following: – Complete response rate determined by investigator assessment – Duration of response determined by investigator assessment – Progression-free survival determined by investigator assessment – Time to response determined by investigator assessment – Overall survival • To evaluate the safety and tolerability of zanubrutinib in patients with CD79B mutant R/R DLBCL when given as monotherapy **Exploratory Objectives** • To evaluate the pharmacokinetics (PK) of zanubrutinib in patients with CD79B mutant R/R DLBCL – Summary of plasma concentrations of zanubrutinib • To evaluate the correlation of clinical/genetic risk factors and clinical outcomes • To explore mechanisms of disease resistance

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Study Design

This single-arm, open-label, multicenter Phase 2 study is designed to assess the efficacy and safety of zanubrutinib in patients with CD79B mutant R/R DLBCL. The primary efficacy endpoint is the overall response rate determined by the investigator assessment. Disease response will be assessed per the Lugano classification (Cheson et al 2014). The primary analysis will take place approximately 6 months after the first dose of the last patient.

Prescreening evaluations of CD79B mutation status by central laboratory will be performed for patients who have histologically confirmed DLBCL and show a trend of lack of efficacy in their current systemic anti-DLBCL treatments, or the trend of disease progression. Only DLBCL patients with centrally confirmed CD79B mutation (except for patients with CD79B mutation locally confirmed and approved by the sponsor) and refractory or relapsed disease as confirmed by investigators are eligible for screening evaluations. Screening evaluations will be performed within 21 days before the first administration of study drug unless noted otherwise.

The treatment period starts with the first day of zanubrutinib administration and continues until the last dose of zanubrutinib has been administered. Zanubrutinib will be administered orally as two 80-mg capsules twice a day (160 mg twice a day) continuously. Each cycle is 28 days in length. Patients will receive zanubrutinib until disease progression, unacceptable toxicity, loss to follow-up, or the end of the study, whichever occurs first.

All patients who permanently discontinue study drug will remain in the study, have a Safety Follow-up Visit, and subsequently commence long-term follow-up.

Safety Follow-up Visit occurs approximately 30 days (± 7 days) after the last dose of zanubrutinib to perform the planned safety assessments and laboratory assessments, and to collect information on alternative anticancer therapy given after the last dose of study drug.

Long-term follow-up includes monitoring survival status, second primary malignances, subsequent therapies for DLBCL, and may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic progression, which will continue until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first.

Study Assessments:

Assessments of DLBCL status during the study include disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen; bone marrow examination; positron emission tomography (PET)-computed tomography (CT) and/or CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated.

Response will be evaluated on the basis of clinical and radiologic evaluations using the Lugano classification. All patients must have a baseline PET-CT and CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated within 21 days before the first dose of study drug. PET-CT scans are required at screening, at Week 12 and Week 24 after treatment, and at the time when complete response (CR) or progressive disease (PD) is suspected. For fluorodeoxyglucose (FDG) non-avid disease, only CT scans will be required for post-baseline visit. Contrast CT will be performed at screening, every 12 weeks for 24 months, and every 24 weeks thereafter until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first. 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. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of PET-CT shall prevail. Bone marrow biopsy and aspirate are required to assess bone marrow involvement of lymphoma for all patients during the screening period, unless they have been performed within 60 days before the first dose of study drug as part of the standard care and there has been no intervening therapy from the time of the biopsy/aspirate until the start of study drug. For patients with bone marrow involvement of lymphoma at baseline, repeated bone marrow biopsy and aspirate are required if CR is suspected. Clinical

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suspicion of disease progression at any time will require radiologic confirmation to be performed promptly, rather than waiting for the next scheduled radiologic assessment. Magnetic resonance imaging (MRI) and a non-contrast chest CT scan may be used instead of contrast CT for patients with serious contrast allergy; whichever method is used should be used consistently.

Safety assessments will include adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Adverse events will be graded for severity per the National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE). Laboratory assessments, including serum chemistry, complete blood count (CBC), coagulation, urinalysis, and pregnancy tests, should be performed at a local certified laboratory. Details for hepatitis B and hepatitis C are listed in Section 5.8.5.

Blood samples will be collected sparsely at predose and 2 hours (± 30 minutes) postdose on Day 1 of Cycle 1 and Cycle 2 to evaluate the exposure of zanubrutinib.

Tumor tissue must be sent to the central laboratory for CD79B mutation status analysis at the Prescreening Visit. For those patients enrolled, other predictive biomarkers will also be determined during screening and correlated with response, resistance, and prognosis. CD79B mutation status in the blood will be assessed. Blood-based biomarker analysis will also be performed to explore their association with response, resistance, and prognosis.

Key Eligibility Criteria

Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of informed consent.
2. Histologically confirmed DLBCL based on the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissue.
3. Positive CD79B mutation confirmed by the central laboratory.
4. Previously received at least 1 line of adequate systemic anti-DLBCL therapy, defined as an anti-CD20 antibody-based chemoimmunotherapy for at least 2 consecutive cycles, unless patients had disease progression before Cycle 2.
5. Relapsed or refractory (R/R) disease before study entry, defined as either:
    a. Recurrent disease after having achieved disease remission (CR or partial response [PR]) at the completion of the latest treatment regimen.
    b. Stable disease or PD at the completion of the latest treatment regimen.
6. Ineligible for high dose therapy/stem cell transplantation, which is defined as meeting any of the following criteria:
    a. Significant organ dysfunction (eg, left ventricular ejection fraction < 50% by echocardiogram or multiple gated acquisition scan [MUGA], diffuse lung capacity for carbon monoxide < 60% predicted by pulmonary function test, creatinine clearance < 70 mL/min shown by nuclear medicine scan or 24-hour urine collection) or comorbidities precluding the use of high dose therapy/stem cell transplantation on the basis of unacceptable risk of treatment-related morbidity.
    b. Failure to achieve CR or PR with salvage therapy.
    c. Failure to collect stem cells or unable to perform stem cell collection as assessed by the investigator.
7. Patients who have completed autologous stem cell transplantation ≥ 100 days before the first dose of zanubrutinib may be enrolled.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

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9. Measurable disease as defined by at least 1 lymph node > 1.5 cm in longest diameter, or at least 1 extranodal lesion that is > 1.0 cm in longest diameter.
10. Adequate hematologic function, defined as:
    a. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L, except for patients with bone marrow involvement in which ANC must be ≥ 0.75 x 10^9/L, independent of growth factor support within 7 days before the first dose of study drug.
    b. Platelet count ≥ 75 x 10^9/L (or ≥ 50 x 10^9/L for patients with bone marrow involvement of lymphoma), independent of growth factor support or transfusion within 7 days before the first dose of study drug.
    c. Hemoglobin > 80 g/L, independent of growth factor support or transfusion within 7 days before the first dose of study drug.
11. Adequate hepatic function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN).
    b. Total bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome, in which case ≤ 5 x ULN is allowed).
12. Adequate renal function, defined as creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]).
13. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN.
14. Female patients of childbearing potential must practice highly effective methods of contraception (Section 5.3) starting from before the first dose of study drug, throughout the study treatment, and for up to 1 month after the last dose of zanubrutinib.
15. Male patients are eligible if abstinent or vasectomized or if they agree to use highly effective contraception (as described in Section 5.3) during the study treatment period and for up to 1 week after the last dose of zanubrutinib.
16. Life expectancy of > 3 months.
17. Able to provide written informed consent and can understand and comply with the requirements of the study.

Exclusion Criteria

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

1. Patients who have NHL other than classical histology DLBCL (DLBCL, not otherwise specified), eg, patients with DLBCL transformed from indolent lymphomas, primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, primary effusion lymphoma, and central nervous system (CNS) lymphoma.
2. History of allogeneic stem cell transplantation or chimeric antigen receptor (CAR) T-cell therapy.
3. Prior exposure to a Bruton tyrosine kinase (BTK) inhibitor.
4. Receipt of the following treatment at the time indicated before the first dose of study drug:
    a. Corticosteroid given with antineoplastic intent within 2 weeks, but a short course (≤ 7 days) of systemic corticosteroid treatment at doses ≤ 20 mg/day prednisone equivalent for control of lymphoma-related symptoms is allowed prior to enrollment provided that it is tapered off within 5 days after initiation of study treatment.
    b. Chemotherapy or radiotherapy within 2 weeks.

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c. Monoclonal antibody within 2 weeks.
d. Investigational therapy within 2 weeks.
e. Chinese patent medicine with antineoplastic intent within 2 weeks.

5. Toxicity of Grade ≥ 2 from prior anticancer therapy (except for alopecia, ANC, hemoglobin and platelets. For ANC, hemoglobin and platelets, please follow inclusion criterion #10).
6. History of other active malignancies within 2 years before study entry, with the exception of (1) adequately treated in-situ carcinoma of the cervix; (2) localized basal cell or squamous cell carcinoma of the skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
7. Clinically significant cardiovascular disease including the following:
   a. Myocardial infarction within 6 months before screening.
   b. Unstable angina within 3 months before screening.
   c. Clinically significant arrhythmia (eg, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes).
   d. QTcF (Fridericia's correction) > 480 msec.
   e. History of second-degree atrioventricular (AV) block Type II or third-degree AV block.
   f. New York Heart Association class 3 or 4 congestive heart failure (see Appendix 3).
   g. Uncontrolled hypertension as indicated by at least 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening.
8. 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.
9. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
10. Inability to swallow capsules or presence of a disease that significantly affects gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
11. Active fungal, bacterial and/or viral infection that requires systemic therapy.
12. Known HIV, or serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but without HBsAg, are eligible if HBV DNA is undetectable (< 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (< 15 IU/mL).
13. Requires ongoing treatment with strong and moderate cytochrome P450 3A (CYP3A) inhibitors or inducers (see Appendix 4). If patients have been on strong or moderate CYP3A inhibitors or inducers in the past, they will not be eligible if the administration was within 7 days (or 5 half-lives of these drugs) before the first dose of study drug.
14. Major surgery within 4 weeks before the first dose of study drug.
15. Live vaccination within 4 weeks before the first dose of study drug.

16. Any medical condition or organ system dysfunction that, in the investigator's opinion, could compromise the patient's safety or put the study at risk.
17. Pregnant or lactating women.

Test Product, Dose, and Mode of Administration

Zanubrutinib will be administered orally as two 80-mg capsules twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Each cycle is 28 days in length.

Statistical Methods

Analysis Sets:

Safety Analysis Set: includes all patients who receive at least one dose of zanubrutinib. The Safety Analysis Set will be used for both safety and efficacy analyses.

PK Analysis Set: includes all patients for whom there is at least one available postdose zanubrutinib PK concentration measurement.

Efficacy Analyses:

Efficacy assessments will use the Lugano classification to assess overall disease response.

Primary Efficacy Analysis:

The primary efficacy endpoint is the overall response rate determined by the investigator assessment, where the overall response rate is defined as the proportion of patients in the Safety Analysis Set whose best overall response is either CR or PR. The best overall response is defined as the best response recorded from the start of zanubrutinib until the data cutoff date or the start of alternative anticancer treatment. Patients who drop out earlier with no post-baseline response assessment (for any reason) will be considered nonresponders for best overall response.

The overall response rate of historical control in this study is 30% (Section 9.2.5.1). A binomial exact test will be performed for hypothesis testing H_0: overall response rate of zanubrutinib = 30% versus H_a: overall response rate of zanubrutinib > 30% in the Safety Analysis Set. If the null hypothesis can be rejected at one-sided significance level of 0.025, it will be concluded that the historical control of 30% can be ruled out. A 2-sided Clopper-Pearson 95% confidence interval (CI) of overall response rate will also be calculated to assess the precision of the estimation.

The primary analysis will take place approximately 6 months after the first dose of the last patient.

Secondary Efficacy Analyses:

The complete response rate determined by investigator assessment will be summarized along with the 2-sided Clopper-Pearson 95% CI.

Duration of response is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. The duration of response will be only summarized for responders. The Kaplan-Meier method will be used to estimate duration of response curves and corresponding quantiles (including the median) (Schemper and Smith 1996). A 2-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The duration of response event-free rates at selected timepoints will be estimated along with the corresponding 95% CI.

Progression-free survival is defined as the time from the starting date of the therapy to the date of first documentation of disease progression or death, whichever occurs first. The Kaplan-Meier method will be used to estimate progression event-free curves and corresponding quantiles (including the median) (Schemper and Smith 1996). A 2-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The progression-free survival probability at selected timepoints will be estimated along with the corresponding 95% CI.

Time to response, defined as time from the starting date of therapy to the date the response criteria are

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first met, will be summarized with descriptive statistics only for responders.

Overall survival, defined as the time from the starting date of the therapy to the date of death due to any reason, will be analyzed similarly as progression-free survival.

Primary and selected secondary endpoints will also be summarized descriptively in specified subgroups and the within group values will be presented in forest plots.

Safety Analyses:

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

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded according to the NCI-CTCAE Version 5.0.

A treatment-emergent adverse event is defined as an adverse event that had an onset date or worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib, or the initiation of any alternative anticancer therapy, whichever comes first. Worsening of an event to Grade 5 beyond day 30 after last dose of study drug of a treatment-emergent adverse event is also considered a treatment-emergent adverse event. The patient incidence of all treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-emergent adverse events of Grade 3 or higher, treatment-emergent adverse events leading to death, and treatment-emergent adverse events leading to treatment discontinuation and dose modification (dose reduction or dose interruption) will be summarized. Multiple occurrences of the same event will be counted once at the maximum severity within a system organ class (SOC) and preferred term (PT). Deaths and cause of deaths will be summarized.

Laboratory test results, vital signs, and their changes from baseline were summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables).

PK Analyses:

Plasma zanubrutinib concentration data will be tabulated and summarized by cycle. Descriptive statistics including means, standard deviations, medians, and ranges as appropriate, will be used for the analysis of plasma zanubrutinib concentrations.

Sample Size:

The sample size of the study is planned based on the level of precision of overall response rate estimate as well as the power of a hypothesis testing against a historical rate. The targeted overall response rate in this study is 50% (Section 1.5.2), which is deemed a clinically meaningful improvement based on a historical control of 30%. Assuming a true overall response rate of 50% in the study population, 66 patients will provide 90% power to reject the null hypothesis of 30% ORR at the one-sided significance level of 0.025. The 95% Clopper-Pearson CI will be (37.4%, 62.6%) with a sample size of 66 patients, when the observed overall response rate is 50%.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABC DLBCL	activated B cell-like diffuse large B-cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
BGB-3111	zanubrutinib
BTK	Bruton tyrosine kinase
CBC	complete blood count
CDx	companion diagnostics
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FL	follicular lymphoma
GCB DLBCL	germinal center B cell-like diffuse large B-cell lymphoma
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IPI	International Prognostic Index

Abbreviation	Definition
IRB	Institutional Review Board
IRC	Independent Review Committee
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QTc	corrected QT interval
R/R	relapsed/refractory
SLL	small lymphocytic lymphoma
SOC	system organ class
ULN	upper limit of normal
WBC	white blood cell
WM	Waldenström macroglobulinemia

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1. INTRODUCTION

1.1. Background Information on DLBCL

Diffuse large B-cell lymphoma (DLBCL) is an aggressive (fast-growing) and high-grade lymphoma that can arise in nodal or extranodal sites, such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. DLBCL arises from a mature B cell and is usually composed of cells resembling centroblasts or immunoblasts, which are 2 distinct types of activated B cells. DLBCL is the most common type of non-Hodgkin lymphoma (NHL) and accounts for 30% to 40% of new diagnoses (Al-Hamadani et al 2015; Teras et al 2016). There were 509,590 new cases of NHL and 248,724 deaths resulting from this disease worldwide in 2018 (Bray et al 2018). The incidence of NHL is increasing in many regions. The age-standardized incidence has increased by 35% in 30 years (1988 to 2007) in England, and a similar trend has been recorded in the United States (US), with an annual percentage increase of 3.7% in the incidence of NHL between 1975 and 1991, and a 0.3% annual increase from 1992 to 2007 (Shankland et al 2012). Based on the data in the registration database of the Chinese Center for Disease Control and Prevention, in 2015, approximately 88,200 new cases of lymphoma and 52,100 death cases occurred in China, and lymphoma ranks 12th in terms of incidence and 11th in terms of mortality among all cancers, respectively (Chen et al 2016). According to one retrospective analysis for lymphoma subtype distribution conducted by the China Lymphoma Study Group, DLBCL makes up about 40.8% of NHL cases and 35.8% of all lymphoma cases (Li et al. 2012). According to current Surveillance Epidemiology and End Results (SEER) data, the median age at diagnosis is 67 years (SEER 2010). DLBCL is usually aggressive, marked by rapidly growing tumors in lymph nodes, spleen, liver, bone marrow, or other organs (Coiffier 2001). A very aggressive malignancy in its untreated natural history, DLBCL is a potentially curable disease, with a significant proportion of patients cured with modern chemoimmunotherapy. Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor (Gisselbrecht 2010) and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies.

DLBCL is staged according to the Ann Arbor classification (Carbone et al 1971); less than one-third patients have Stage 1 or 2 disease at diagnosis, one-third present with bulky disease (> 7.5 cm), about 40% have extra-nodal involvement, and 20% have marrow involvement (Moller et al 2004). The International Prognostic Index (IPI), proposed in 1993, predicts the survival of patients with NHL. The IPI consists of 5 factors: patient age > 60 years, lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status > 2, > 2 extranodal sites, and Stage 3 or 4 disease. Patients are stratified into 4 risk groups: low risk (1 factor), low-intermediate risk (2 factors), high-intermediate risk (3 factors), and high risk (4-5 factors). Five-year survival rates are 73%, 51%, 43%, and 26% for the 4 groups, respectively. Regarding applicability of the IPI in the era of modern chemoimmunotherapy (eg, R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone]), a recent report of a large series of patients treated with rituximab-based regimens found that the IPI remains predictive for disease-free and overall survival (Shipp et al 1993).

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DLBCL has distinct morphological and clinicopathological subtypes. The common morphological subtypes are centroblastic, immunoblastic, and anaplastic. Centroblasts are large noncleaved cells with round or oval nuclei associated with good prognosis, whereas immunoblasts are large cells with prominent nucleoli and plasmacytoid features. Plasmablastic lymphoma is a morphological variant that is immunophenotypically distinct from other variants.

Biological studies have shown that DLBCL is not a single disease but a group of disorders with specific signaling programs from the perspective of clinicopathology. In 2000, gene expression profiling (GEP) of 96 normal and DLBCL lymphocytes was used to identify 3 different subtypes of disease based on cell of origin (COO) (Alizadeh et al 2000). The 3 subtypes are: the germinal center B cell-like (GCB) subtype (which resembles the GEP of normal GCBs), the activated B cell-like (ABC) subtype (which resembles normal ABCs), and unclassifiable disease. In recent years, according to the Hans algorithm, DLBCL can be categorized into GCB and non-GCB phenotypes by the immunohistochemical expression pattern of CD10, B-cell lymphoma 6 (BCL6), and multiple myeloma oncogene 1 (MUM1) (Xie et al 2015; Meyer et al 2011).

In parallel to the COO studies, the subtypes of DLBCL based on molecular features have also been found to have prognostic impacts. DLBCL is a highly heterogeneous lymphoid neoplasm with variations in gene expression profiles and genetic alterations, which lead to substantial variations in clinical course and response to therapy. The advent of high-throughput genome sequencing platforms, and especially whole-exome sequencing, has helped to define the genetic landscape of DLBCL. In the past 10 years, numerous studies have identified many genetic alterations in DLBCL, some of which are specific to B-cell lymphomas, whereas others can also be observed in other types of cancer. These aberrations result in the altered activation of a wide range of signalling pathways and other cellular processes, including those involved in B-cell differentiation, B-cell receptor signalling, activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, apoptosis and epigenetic regulation. Among these mutations, some potential therapeutic targets have been identified, such as MYD88, CD79A, CD79B, EZH2, and BCL2. Patients with relapsed/refractory (R/R) DLBCL contains a CD79B mutation are the selected biomarker-driven population for this Phase 2 study.

CD79B Mutant DLBCL

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. Antigen specificity of the B-cell receptor is provided by surface immunoglobulin, but signaling is mediated by 2 associated proteins,CD79A (Ig-a) and CD79B (Ig-b) (Dal Porto et al 2004). The CD79A-CD79B heterodimer is a scaffold for the assembly and membrane expression of the B-cell receptor and also initiates downstream signaling to the NF-κB, phosphatidylinositol-3-OH kinase, extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase and nuclear factor of activated T cells (NF-AT) pathways. Engagement of the B-cell receptor by antigen induces Src-family kinases to phosphorylate tyrosines in the intracellular immunotyrosine-based activation motif (ITAM) of CD79A and CD79B (Davis et al 2010).

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In mouse B cells, mutations in the CD79A or CD79B ITAM tyrosine residues elevate surface B-cell receptor expression by inhibiting receptor internalization (Gazumyan et al 2006). Interruption of chronic active B-cell receptor signaling with dasatinib, a kinase inhibitor approved for the treatment of chronic myelogenous leukemia, inhibits Src-family kinases and Bruton tyrosine kinase (BTK) increased surface B-cell receptor expression in ABC DLBCL cells with wild-type but not mutant CD79B. Hence, one function of the CD79 mutations is to maintain surface B-cell receptor expression in the face of chronic active B-cell receptor signaling (Davis et al 2010).

Studies that examined the association between specific mutations and survival among all DLBCLs found that CD79B mutations were strongly associated with poorer survival (Reddy et al 2017). In one study, 574 DLBCL biopsy samples were analyzed using exome and transcriptome sequencing, array-based DNA copy-number analysis, and targeted amplicon resequencing of 372 genes to identify genes with recurrent aberrations. CD79B mutations were found in 15.5% of all DLBCL samples, of which 26.8% were found in the ABC subtype, 1.9% in the GCB subtype, and 6.1% in the unclassified subtype (Schmitz et al 2018). In a Phase 1/2 study of ibrutinib, 9/38 (23.7%) patients with ABC DLBCL were found to have CD79B mutation (Wilson et al 2015). And in zanubrutinib studies, 21/77 (27.3%) patients with non-GCB DLBCL were found to have CD79B mutation. Thus, it is estimated that a CD79B mutation is present in approximately 25% of patients with non-GCB/ABC DLBCL, and the percentage of CD79B mutation in all patients with DLBCL is estimated to be approximately 15%. Based on the fact that SEER and GLOBOCAN 2018 data suggest a NHL incidence of 88,090 cases per year in China and 74,680 cases in the USA, and that the percentage of DLBCL in NHL is approximately 33%, it can be estimated that the incidence of CD79B mutant DLBCL is about 4000 per year in China and the USA each.

1.2. Current Treatment of DLBCL and Unmet Clinical Needs

DLBCL is a heterogeneous clinicopathologic entity accounting for 30% to 40% of NHL cases. Despite recent advances, there is still an unmet need for better therapies, especially R/R DLBCL (Witzig et al 2015).

In clinical practice, the treatment decision is based on various factors such as the age of the patient, disease stage, presence of bulky disease, and IPI. After rituximab was introduced to treat DLBCL, the current first-line treatment is R-CHOP regimen. Due to the complex pathogenesis of DLBCL, 30% to 40% patients develop R/R disease and have poor outcomes despite recent progress in improving prognosis. Patients might fail first-line chemoimmunotherapy or salvage therapy followed by high dose therapy and bone marrow transplantation; only 10% to 20% of patients have long-term disease-free survival (Crump et al 2017). Patients with primary refractory disease or those who relapse within 12 months have a dismal outcome with the current standard of care; the median overall survival is about 5 to 6 months (Friedberg 2011). CD79B mutation is detected mainly in ABC DLBCL, and it is reported that, in patients with newly diagnosed and R/R DLBCL, ABC DLBCL and non-GCB DLBCL were associated with worse outcomes than GCB DLBCL, with shorter progression-free survival and overall survival (Batlle-López et al 2016; Hernandez-Ilizaliturri et al 2011; Thieblemont et al 2011).

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Moreover, patients may be ineligible for bone marrow transplantation because of age or comorbidities. Patients who relapse following autologous bone marrow transplantation also have poor outcomes with limited treatment options. Both the US National Comprehensive Cancer Network (NCCN) (NCCN 2020) and the European Society for Medical Oncology (ESMO) recommend inclusion in a clinical study whenever possible (Tilly et al 2015).

Multiple drugs are currently under clinical investigation for DLBCL, including alternative kinase inhibitors (targeting BTK, mammalian target of rapamycin, and phosphatidylinositol-3 kinase [PI3K]), immunotherapies (including lenalidomide and chimeric antigen receptor T cells), and other targeted agents (such as venetoclax, a BCL 2 inhibitor). Chimeric antigen receptor (CAR) T-cell therapy shows promise in these patients (Brudno and Kochenderfer 2018); however, this therapy is limited to certain treatment centers and may have significant toxicity which may be intolerable for some patients. Lenalidomide and avadomide, two immunomodulatory agents with pleiotropic antitumor activity, showed an overall response rate of 27.5% and 29%, respectively, in the patients with R/R DLBCL (Czuczman et al 2017, Carpio et al 2020). Immune checkpoint blockade with the anti-programmed death-1 (anti-PD1) monoclonal antibody nivolumab demonstrated a low overall response rate in patients with R/R DLBCL who were ineligible for autologous hematopoietic cell transplantation (auto-HCT) or who experienced treatment failure with auto-HCT in a Phase 2 study (overall response rate of 3% and 10%, respectively) (Ansell et al 2019). Panobinostat, a pan histone deacetylase inhibitor, exhibited an overall response rate of 29% in R/R DLBCL patients, and combination of rituximab did not increase the overall response rate (26%) (Assouline et al 2016). Selinexor, an exportin 1 (XPO1) inhibitor, exhibited an overall response rate of 29% in patients with R/R DLBCL; however, toxicities were difficult to tolerate and necessitated close monitoring and supportive care (Kasamon et al 2021, Maerevoet et al 2021). For antibody-drug conjugates, coltuximab ravtansine showed an overall response rate of 31.1% in R/R DLBCL patients (Coiffier et al 2016), and pinatuzumab vedotin exhibited objective responses in 9/25 DLBCL patients (Advani et al 2017). Tafasitamab (MOR208), an anti-CD19 antibody, showed an overall response of 26% in 35 R/R DLBCL patients, with a duration of response of 20.1 months and median progression-free survival of 2.7 months after a median follow-up of 21 months (Jurczak et al 2018). Mosunetuzumab and RG6026 are bi-specific CD20/CD3 antibodies that redirect cytotoxicity of endogenous T cells against malignant B cells by simultaneously binding to CD3 on T cells and to CD20 on B cells. A Phase 1 study examining mosunetuzumab in patients with R/R transformed follicular lymphoma (FL) or DLBCL is ongoing (Budde et al 2018). Preliminary results of 55 evaluated patients reported overall response and complete response rates of 33% and 21% respectively. The Phase 1 study of RG6026 also demonstrated an overall response rate of 33% in 64 evaluable R/R aggressive NHL patients (47 with DLBCL) (Hutchings et al 2018). These chemo-free therapies showed only modest efficacy results, therefore, there is a substantial unmet need for novel treatments for relapsed or refractory DLBCL.

1.3. Bruton Tyrosine Kinase Therapy With DLBCL

The B-cell receptor consists of an antigen-specific immunoglobulin that recognizes a specific antigen and CD79 heterodimers that are responsible for the initiation of B-cell receptor signal transduction. B-cell receptor signaling is essential for normal B-cell development,

differentiation, function, and survival (Dal Porto et al 2004; Niiro and Clark 2002). The aberrant B-cell receptor pathway is implicated in the pathogenesis of several B-cell malignancies, including DLBCL, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), FL, and Waldenström macroglobulinemia (WM) (Rickert 2013).

Bruton tyrosine kinase (BTK), an intermediary in the B-cell receptor signaling pathway, has been validated as a therapeutic target based on clinical data from BTK inhibitor-treated patients with a variety of B-cell malignancies characterized by constitutive B-cell receptor activation (Cameron and Sanford 2014). As a member of the family of cytoplasmic tyrosine kinases expressed in hepatocellular carcinoma (TEC), BTK is a critical component of the B-cell receptor signaling cascade. BTK is predominantly expressed in B lymphocytes at various stages of development. BTK activation in B cells initiates a series of signaling events, including recruitment of BTK to the plasma membrane, autophosphorylation at Tyr223, activation of phospholipase $C\gamma_2$ ($PLC\gamma2$), subsequent NF-κB activation, and expression of genes involved in proliferation and survival (Humphries et al 2004; Advani et al 2013; Petro and Khan 2001).

Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Efficacy of BTK inhibitors has been primarily demonstrated in a proof-of-concept study in patients with B-cell malignancies, with a well-tolerated toxicity profile and quality of life.

Ibrutinib, the first-in-class BTK inhibitor has demonstrated promising activity in B-cell receptor-driven B-cell malignancies and is approved by the US Food and Drug Administration (FDA). Ibrutinib is an orally administered selective and covalent inhibitor of BTK that reduces NF-κB pathway signaling and might therefore be effective for patients with the ABC subtype of DCBCL. A Phase 1/2 study examined the efficacy and safety of ibrutinib in 80 patients with R/R DLBCL, including 38 patients with ABC DLBCL and 20 patients with GCB DLBCL (Wilson et al 2015). Two thirds of the patients were refractory to chemotherapy and had received a median of 3 (ABC DLBCL group) or 3.5 (GCB DLBCL group) prior regimens. An autologous stem cell transplantation had been performed in 13% of patients in the ABC DLBCL group and in 30% of patients in the GCB DLBCL group. The overall response rate was 25%, with a higher overall response rate in the ABC DLBCL group than in the GCB DLBCL group (37% versus 5%, $p = 0.0106$). The duration of response in patients with the ABC DLBCL subtype was 4.8 months. After a median follow-up of 11.5 months, median progression-free survival and overall survival were 1.6 and 6.4 months in all patients, respectively. The most frequent adverse events were fatigue (40%), diarrhea (38%), and nausea (30%).

Acalabrutinib (ACP-196) is a second-generation BTK inhibitor with increased target selectivity and potency compared to ibrutinib. It was reported that overall response rate for R/R de novo DLBCL patients of acalabrutinib was 24% (5/21; 19% complete response [CR]). NanoString subtyping conducted on 15 patients revealed 5 GCB, 9 ABC, and 1 unclassified DLBCL. Common adverse events (any grade) were diarrhea (43%), fatigue (43%), anemia (29%), cough (29%) and dizziness (29%); common Grade 3/4 adverse events were anemia (24%), fatigue (10%) and abdominal pain (10%). Three patients experienced Grade 5 adverse events (respiratory failure, meningeal progression, and sepsis); none were drug related (Dyer et al 2018).

From the preliminary efficacy results previously noted, recent BTK-inhibitor monotherapy demonstrated modest efficacy results in R/R DLBCL patients. However, given the important

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role of BTK inhibitors with B-cell malignancies and activation of the B-cell receptor pathway and downstream NK-κB pathway, the structure optimization of BTK inhibitors or combined therapy with other treatment agents will bring more benefits in the control of treatment outcome for DLBCL.

1.4. Background Information on Zanubrutinib (BGB-3111)

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

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

1.4.1. Nonclinical Data for Zanubrutinib

Summaries of nonclinical studies are provided below. For more detailed information please refer to the zanubrutinib Investigator's Brochure.

Zanubrutinib is a potent, specific and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomole per liter (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 fluorescent-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 the TMD-8 DLBCL subcutaneous xenograft model. In a PK/pharmacodynamic study, oral administration of zanubrutinib resulted in time-dependent occupancy of BTK in mice blood and in spleen, 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

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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 not a time-dependent CYP inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Zanubrutinib is not an inducer of CYP1A2 but shows induction potential for CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A. Zanubrutinib is not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 2, organic anion transporter (OAT) 1, and OAT3, but is likely to be a substrate of P-glycoprotein (P-gp). Additionally, zanubrutinib is predicted not to cause clinically relevant inhibition of transporters, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2.

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.

1.4.2. Clinical Pharmacology

In the first-in-human, Phase 1/2 study, BGB-3111-AU-003, the PK of zanubrutinib was linear between 40 mg and 320 mg once a day administered orally. The absorption of zanubrutinib is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 2 to 4 hours, with minimal accumulation observed after repeated dosing. Results from a food effect study (BGB-3111-103) showed that dosing with food (high-fat or low-fat meal) did not cause any significantly meaningful effects on the area under plasma concentration-time curve (AUC) of zanubrutinib; therefore, zanubrutinib can be administered with or without food.

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

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that coadministration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once a day

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for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$ and 12.6-fold for maximum plasma concentration (C_{max}) in healthy subjects. Co-administration of zanubrutinib with strong CYP3A inhibitor itraconazole (200 mg once a day for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$ and by 2.6-fold for C_{max}. Additionally, physiologically based pharmacokinetic (PBPK) simulations suggest that coadministration of multiple doses of a moderate CYP3A inhibitor (eg, fluconazole, diltiazem, and erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. PBPK simulations suggest that a moderate CYP3A inducer (eg, efavirenz) may decrease the C_{max} and AUC of zanubrutinib by approximately 2- to 3-fold. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

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-glycoprotein (P-gp [digoxin]), BCRP (rosuvastatin) using a cocktail approach. The results showed that zanubrutinib does not affect drugs metabolized by CYP2C9 (warfarin) or transported by BCRP (rosuvastatin). Zanubrutinib had a weak induction effect on CYP3A and CYP2C19 enzymes. 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}.

For more detailed information on the clinical experience for zanubrutinib, please refer to the zanubrutinib Investigator's Brochure.

1.4.3. Preliminary Efficacy and Safety Data with Zanubrutinib in DLBCL Patients

1.4.3.1. Phase 1/2 Study BGB-3111-AU-003

Study BGB-3111-AU-003 was a global, first-in-human, Phase 1/2, open-label, multiple-dose, dose-escalation and dose-expansion study of zanubrutinib that was initiated in Australia in August 2014. The study consisted of 2 parts. In Part 1, the primary objectives were to determine the safety and tolerability of zanubrutinib in patients with various B-cell malignancies (CLL/small lymphocytic lymphoma [SLL], NHL, and WM) and to determine the recommended Phase 2 dose. In Part 2, the primary objective was to further assess the safety and tolerability of zanubrutinib in patients with B-cell malignancies, while a secondary objective was to assess the antitumor activity of zanubrutinib at the recommended Phase 2 dose.

As of the data cutoff date (31 March 2021), 385 patients had been dosed in this clinical study. Dosing of the first patient occurred on 16 September 2014. A total of 45 DLBCL patients were enrolled in the BGB-3111-AU-003 study, 66.7% of which were male, with 55.6% of these patients ≥ 65 years old; 86.7% of DLBCL patients had an ECOG score of 0 to 1.

As of 31 March 2021, 43/45 (95.6%) DLBCL patients had experienced ≥ 1 treatment-emergent adverse event while on study, 23 (51.1%) of which were considered as related to zanubrutinib, and 29/45 (64.4%) had reported ≥ 1 serious adverse event. The most frequent treatment-emergent adverse events of the DLBCL cohort were pyrexia (26.7%), cough (24.4%), constipation (22.2%), upper respiratory tract infection (20.0%), nausea (20.0%), fatigue (17.8%),

back pain (15.6%), diarrhea (13.3%), pneumonia (13.3%), anemia (11.1%), contusion (11.1%), pruritus (11.1%), and hypertension (11.1%). As reported by Tam et al 2019 with a data cutoff of 15 September 2017, 99 patients with NHL had been enrolled, including 27 DLBCL patients, and of which 26 patients were evaluable for efficacy. After a median follow-up of 5.6 months (range: 0.1 to 31.9 months) for the aggressive lymphoma group (DLBCL and MCL), the overall response rate was 62% (36/58), with a complete response rate of 21% (12/58).

1.4.3.2. Phase 2 Study BGB-3111-207

Study BGB-3111-207 was a single-arm, open-label, multicenter Phase 2 study being conducted in China in patients with histologically documented non-GCB-type DLBCL who had no response or relapsed after ≥ 1 prior treatment regimens including rituximab and anthracycline-based chemotherapy. Patients must also have been ineligible for intensive chemotherapy and hematopoietic stem cell transplantation.

The primary objective was to evaluate the efficacy of zanubrutinib administered orally at a dose of 160 mg twice a day in patients with R/R non-GCB DLBCL. Secondary objectives included the evaluation of the safety and tolerability of zanubrutinib administered orally at a dose of 160 mg twice a day and evaluation of the efficacy of zanubrutinib as measured by duration of response, progression free survival, and time to response.

Dosing of the first patient in this study occurred on 30 June 2017. As of the 03 September 2020 data cutoff date, a total of 41 patients had been dosed. The median age of patients was 62.0 years (range: 28 to 75 years). Most patients were male (61.0%) and had a baseline ECOG score of 0 or 1 (24.4% patients and 65.9% patients, respectively).

An overall response rate of 29.3% (95% confidence interval [CI]: 16.13% to 45.54%) was observed, with a complete response rate of 17.1% (95% CI: 7.15% to 32.06%). Median progression-free survival for this study was 2.8 months (95% CI: 2.56 to 5.45 months), with estimated progression-free survival event-free rates of 45.9%, 21.6%, and 10.1% at 3, 6, and 12 months, respectively. Median overall survival for this study was 8.4 months (95% CI: 4.8 months to not estimable [NE]), with estimated overall survival event-free rates at 3, 6, and 12 months of 89.8%, 58.1%, and 35.6%, respectively.

As of the 03 September 2020 data cutoff date, 36/41 patients (87.8%) had experienced at least 1 treatment-emergent adverse event while on study. The most frequent treatment-emergent adverse events were neutrophil count decreased (22.0%), hypokalaemia (17.1%), pneumonia (12.2%), and platelet count decreased (12.2%). As of the data cutoff date, 12/41 patients (29.3%) had experienced a serious adverse event. The most frequently reported serious adverse event was pneumonia (3 patients, 7.3%).

1.4.3.3. Phase 2 Study BGB-3111-213

Study BGB-3111-213 was an open-label, multicenter study evaluating the safety and efficacy of zanubrutinib in combination with rituximab in patients with either R/R non-GCB DLBCL or R/R FL or R/R marginal zone lymphoma (MZL). Zanubrutinib was administered orally at 160 mg twice a day. Rituximab was administered at 375 mg/m^2 intravenously on Days 1, 8, 15, and 22 of Cycle 1, and on Day 1 of Cycles 4, 6, 8, and 10. Zanubrutinib was administered ≥ 30 minutes prior to the initiation of the rituximab infusion. All patients were to receive zanubrutinib in

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combination with rituximab for Cycles 1 to 10, followed by zanubrutinib monotherapy starting at Cycle 11 until disease progression, unacceptable toxicity or death, withdrawal of consent, or the study was terminated by the sponsor for final analysis.

The primary objective was to evaluate efficacy in these patient populations, as measured by overall response rate assessed by the investigator. The secondary objectives were to evaluate other efficacy measures as well as the safety and tolerability of the study drug combination.

Dosing of the first patient in this study occurred on 04 January 2018. As of the 23 September 2020 data cutoff, a total of 41 patients had been dosed, including 20 non-GCB DLBCL patients. In the non-GCB DLBCL cohort, 65% of patients were male, 30% of patients were ≥ 65 years old, and 35% of patients had a baseline ECOG score of 1 to 2.

The median follow-up duration was 9.5 months for the non-GCB DLBCL cohort at the efficacy data cutoff date. The overall response rate was 35.0% in the non-GCB DLBCL cohort. Two (10.0%) non-GCB DLBCL patients achieved CR. In the non-GCB DLBCL cohort, the median duration of response was 8.79 months, and the median progression-free survival was 3.38 months. The estimated progression-free survival event-free rate at 12 months was 17.4% for the non-GCB DLBCL cohort.

As of the safety data cutoff date of 23 September 2020, all of the patients in the non-GCB DLBCL cohort had experienced at least 1 treatment-emergent adverse event while on study. The most frequent treatment-emergent adverse events reported in the non-GCB DLBCL cohort were white blood cell count decreased (25.0%), abdominal pain upper (25.0%), anemia (20.0%), neutrophil count decreased (20.0%), alanine aminotransferase increased (15.0%), platelet count decreased (15.0%), aspartate aminotransferase increased (10.0%), and pneumonia (10.0%). Three fatal treatment-emergent adverse events were reported in the non-GCB DLBCL cohort (dyspnea, death in setting of disease progression, and suicide). Treatment-emergent adverse events led to treatment discontinuation in 5 non-GCB DLBCL patients.

1.4.3.4. Phase 1 Study BGB-3111-GA101-Study-001

Study BGB-3111-GA101-Study-001 was a global Phase 1b, open-label, multicenter study with a combined zanubrutinib and obinutuzumab treatment in patients with B-cell malignancies, specifically, CLL/SLL, WM, FL, MCL, MZL, and DLBCL. This was a 2-part study; Part 1 was focused on safety evaluation, and Part 2 included indication-specific expansion cohorts. Dosing of the first patient in this study occurred on 13 January 2016. As of the 02 September 2020 data cutoff, a total of 119 patients had been dosed, including 23 patients with DLBCL. About half of these DLBCL patients were male (56.5%), and the median age was 74 years old, with most having an ECOG score of 0 or 1 (78.2%).

All patients with DLBCL had experienced ≥ 1 treatment-emergent adverse event. The most frequent treatment-emergent adverse events reported among the DLBCL patients were fatigue (43.5%), pyrexia (34.8%), diarrhea (30.4%), upper respiratory tract infection (26.1%), neutropenia (26.1%), cough (17.4%), contusion (17.4%), oedema peripheral (17.4%), constipation (17.4%), urinary tract infection (17.4%), hematuria (17.4%), nausea (13.0%), rash (13.0%), dizziness (13.0%), and cellulitis (13.0%). Among the DLBCL patients, 15/23 (65.2%) had experienced ≥ 1 treatment-emergent serious adverse event.

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Please refer to the zanubrutinib Investigator's Brochure for more preliminary efficacy and safety data.

1.5. Study Rationales

1.5.1. Rationale for Selection of Dose

Dose selection of zanubrutinib was based on results from the Phase 1/2 dose-finding Study BGB-3111-AU-003, which evaluated the pharmacokinetics/pharmacodynamics, safety, and preliminary efficacy of zanubrutinib at doses from 40 mg to 320 mg once a day and 160 mg twice a day. A maximum tolerated dose was not reached in Study BGB-3111-AU-003, and no dose-limiting toxicity was observed during the dose escalation part of the study.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice a day and 320 mg once a day (Tam et al 2015). At the 160 mg twice a day dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including CLL, 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 experience at doses of 160 mg twice a day and 320 mg once a day, with both schedules showing a high level of activity without compromising the tolerability profile as compared to lower doses of zanubrutinib. Therefore, 160 mg administered orally twice a day has been selected as the recommended Phase 2 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.

Since zanubrutinib has been studied at the dose of 160 mg twice a day on a continuous daily dosing schedule and is well tolerated, it will be administered daily until disease progression or unacceptable toxicity.

1.5.2. Rationale for the Therapy

DLBCLs are neoplasms of medium or large B-lymphoid cells with a diffuse growth pattern. DLBCL encompasses many different disease entities with distinct clinical, pathological and biological features. Further elaboration of the genetics of DLBCL will not only improve our understanding of disease pathogenesis but also provide further insight into disease classification, prognostication and therapeutic targets. Patients in whom R/R DLBCL contains a CD79B mutation are the selected biomarker-driven population for this study.

Treatment with BTK inhibitors such as ibrutinib has demonstrated responses in patients with various B-cell malignancies including CLL/SLL, MCL, DLBCL, FL, MZL, and WM. The CD79B mutation may be predictive of BTK inhibitor sensitivity in the DLBCL. It has been reported that CD79B mutant DLBCL cell lines are sensitive to ibrutinib. It was observed that gain-of-function mutations targeting the B-cell receptor subunit CD79B were in 23% of ABC DLBCL biopsy samples. Among patients with CD79B mutations, the response rate to ibrutinib was 55.6% (5/9). Tumors with CD79B mutations responded frequently to ibrutinib, albeit to

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varying degrees and durations (Wilson et al 2015). The compared efficacy data of ibrutinib and zanubrutinib for patients with ABC/non-GCB DLBCL and CD79B mutant/wild-type ABC/non-GCB DLBCL are listed in Table 1. In general, approximately 50% of the overall response rate is observed in CD79B mutant ABC/non-GCB DLBCL patients by BTK inhibitors monotherapy, while the overall response rate for ABC/non-GCB DLBCL patients is approximately 30%.

Table 1: Overall Response Rates of BTK Inhibitors in CD79B Mutant/Wild-type ABC/Non-GCB DLBCL Patients

Response/Patients Overall response rate (%)	Zanubrutinib [a] (Non-GCB)						Ibrutinib [b] (ABC)	
	Mono		Combo		Total		Mono	
All Non-GCB DLBCL	24/79	30.4%	12/42	28.6%	36/121	29.8%	14/38	36.8%
NGS Available Non-GCB DLBCL	18/44	40.9%	11/33	33.3%	29/77	37.7%	14/38	36.8%
CD79B Mutant	9/17	52.9%	6/8	75.0%	15/25	60.0%	5/9	55.6%
CD79B Wild-type	9/27	33.3%	5/25	20.0%	14/52	26.9%	9/29	31.0%
P Value (CD79B Mutant versus Wild-type)	0.1977		0.0041		0.0050		NA	
Difference in overall response rate (95% CI)	19.6% (-10.20%, 46.87%)		55.0% (15.75%,78.76%)		33.1% (9.60%,53.57%)		NA	

Abbreviations: ABC, activated B cell-like; CI, confidence interval; DLBCL, diffuse large B cell lymphoma; GCB, germinal center B cell-like; NA, not applicable; NGS, next-generation sequencing.
Note:
a. BeiGene internal results from studies of BGB-3111-207 (data cutoff date: 31 August 2019), BGB-3111-213 (data cutoff date: 31 May 2019), BGB-3111-AU-003 (data cutoff date: 09 September 2019), and BGB-3111-GA101-Study-001 (data cutoff date: 31 August 2019).
b. Wilson et al 2015.

Ibrutinib and acalabrutinib exhibit significant clinical activity in several B-cell malignancies, while both demonstrate modest efficacy in relapsed DLBCL as a single treatment agent. Clinical efficacy of ibrutinib as a single agent in patients with relapsed DLBCL was modest (overall response rate of 23%) (Younes et al 2017). Acalabrutinib (ACP-196) is a second-generation BTK inhibitor with increased target selectivity and potency compared to ibrutinib. Clinical efficacy of acalabrutinib monotherapy in patients with R/R DLBCL was also modest (overall response rate of 24%) (Dyer et al 2018).

Zanubrutinib, compared to ibrutinib, is a more potent, more specific new-generation BTK inhibitor that has demonstrated a well-tolerated and acceptable safety profile. Furthermore, compared to ibrutinib, zanubrutinib is more selective against off-target kinases including ITK.

In light of the preliminary efficacy and safety data of the ongoing global and China studies of zanubrutinib in B-cell malignancies, the preliminary efficacy as well as safety, tolerability, and PK of zanubrutinib in CD79B mutant DLBCL 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 requirements.

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1.6. Benefit-Risk Assessment

As of the data cutoff date of 13 November 2023, approximately 3030 patients have been enrolled worldwide in completed and ongoing clinical studies evaluating zanubrutinib in B-cell malignancies and received at least 1 dose of zanubrutinib either as monotherapy or in combination with another agent. As demonstrated by clinical data obtained to date, zanubrutinib is a highly selective and orally bioavailable BTK inhibitor that not only achieves high systemic exposure for complete BTK occupancy in the blood and lymph nodes but also remains highly tolerable, despite its exposure and occupancy advantages. When examined in sum, safety and efficacy findings in patients with B-cell malignancies demonstrate that zanubrutinib is well tolerated and has substantial activity against B-cell malignancies, suggesting that studies of zanubrutinib are warranted for patients with lymphoma. BTK inhibitor ibrutinib have been approved by a number of countries for the treatment of CLL/SLL, MCL, WM, and MZL. Zanubrutinib, a new generation BTK inhibitor, has a higher selectivity and stronger inhibitory abilities compared to ibrutinib, and is likely to inhibit tumor growth more effectively in clinical practice.

Available data for zanubrutinib in patients with B-cell malignancies support a positive benefit-risk profile for the use of zanubrutinib as investigational agents to develop new treatment options for patients with CD79B mutant R/R DLBCL.

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2. STUDY OBJECTIVES

Primary Objective

- To evaluate the efficacy of zanubrutinib in patients with CD79B mutant R/R DLBCL, as measured by overall response rate determined by the investigator assessment in accordance with the 2014 modification of the International Working Group on non-Hodgkin lymphoma (NHL) Criteria (hereafter referred to as the Lugano classification) (Cheson et al 2014).

Secondary Objectives

- To evaluate the efficacy of zanubrutinib in patients with CD79B mutant R/R DLBCL, as measured by the following:
  - Complete response rate determined by investigator assessment
  - Duration of response determined by investigator assessment
  - Progression-free survival determined by investigator assessment
  - Time to response determined by investigator assessment
  - Overall survival
- To evaluate the safety and tolerability of zanubrutinib in patients with CD79B mutant R/R DLBCL when given as monotherapy

Exploratory Objectives

- To evaluate the PK of zanubrutinib in patients with CD79B mutant R/R DLBCL
  - Summary of plasma concentrations of zanubrutinib
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes
- To explore mechanisms of disease resistance

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3. STUDY DESIGN

3.1. Summary of Study Design

This single-arm, open-label, multicenter Phase 2 study is designed to assess the efficacy and safety of zanubrutinib in patients with CD79B mutant R/R DLBCL. Patients enrolled in this study should have histologically confirmed DLBCL and central laboratory confirmed positive CD79B mutation. The patients need to have received at least 1 line of adequate systemic anti-DLBCL therapy (ie, anti-CD20 antibody-based chemoimmunotherapy) for at least 2 consecutive cycles, unless who had disease progression before Cycle 2. The patients should be also ineligible for high dose therapy/stem cell transplantation due to comorbidities or failure for salvage therapy and stem cell collection (or unable to perform stem cell collection as assessed by the investigator).

The primary efficacy endpoint is the overall response rate determined by the investigator assessment. Disease response will be assessed per the Lugano classification (Cheson et al 2014, Appendix 2). The primary analysis will take place approximately 6 months after the first dose of the last patient.

Prescreening evaluations of CD79B mutation status by central laboratory will be performed for the patients who have histologically confirmed DLBCL and show the trend of lack of efficacy in their current systemic anti-DLBCL treatments, or the trend of disease progression. Tumor tissue will be collected and sent to the central laboratory for CD79B mutation confirmation. A separate prescreening informed consent form must be signed. Only DLBCL patients with centrally confirmed CD79B mutation (except for patients with CD79B mutation locally confirmed and approved by the sponsor) and refractory or relapsed disease as confirmed by investigators are eligible for screening evaluations. For the DLBCL patients who were tested as CD79B mutant by local laboratories should provide the reports to the sponsor for review, and the tumor tissue are still required to send to the central laboratory. Once the local report results on CD79B mutation are accepted by the sponsor, these patients are eligible for screening evaluations with no need to wait for the central laboratory results. Refer to Section 5.4.1 for detailed information.

Screening evaluations will be performed within 21 days before the first administration of study drug unless noted otherwise. Patients who agree to participate will sign the informed consent form (ICF) before any study-specific screening evaluations. The schema and Schedule of Assessments for this study are presented in Figure 1 and Appendix 1, respectively.

The treatment period starts with the first day of zanubrutinib administration and continues until the last dose of zanubrutinib has been administered. Zanubrutinib will be administered orally as two 80-mg capsules twice a day (160 mg twice a day) continuously. Each cycle is 28 days in length. Patients will receive zanubrutinib until disease progression, unacceptable toxicity, loss to follow-up, or the end of the study, whichever occurs first.

All patients who permanently discontinue study drug will remain in the study, have a Safety Follow-up Visit, and subsequently commence long-term follow-up.

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Safety Follow-up Visit occurs approximately 30 days (± 7 days) after the last dose of zanubrutinib to perform the planned safety assessments and laboratory assessments, and to collect information on alternative anticancer therapy given after the last dose of study drug.

Long-term follow-up includes monitoring survival status, second primary malignances, subsequent therapies for DLBCL, and may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic progression, which will continue until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first.

Study Assessments

Assessments of DLBCL status during the study include disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen; bone marrow examination; positron emission tomography (PET)-computed tomography (CT) and/or CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated. For details about study procedures, see Section 5 and Appendix 1.

Response will be evaluated on the basis of clinical and radiologic evaluations using the Lugano classification. All patients must have a baseline PET-CT and CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated within 21 days before the first dose of study drug. PET-CT scans are required at screening, at Week 12 and Week 24 after treatment, and at the time when CR or progressive disease (PD) is suspected. For fluorodeoxyglucose (FDG) non-avid disease, only CT scans will be required for post-baseline visit. Contrast CT will be performed at screening, every 12 weeks for 24 months, and every 24 weeks thereafter until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first. 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. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of PET-CT shall prevail. Bone marrow biopsy and aspirate are required to assess bone marrow involvement of lymphoma for all patients during the screening period, unless they have been performed within 60 days before the first dose of study drug as part of the standard care and there has been no intervening therapy from the time of the biopsy/aspirate until the start of study drug. For patients with bone marrow involvement of lymphoma at baseline, repeated bone marrow biopsy and aspirate are required if CR is suspected. Clinical suspicion of disease progression at any time will require radiologic confirmation to be performed promptly, rather than waiting for the next scheduled radiologic assessment. Magnetic resonance imaging (MRI) and a non-contrast chest CT scan may be used instead of contrast CT for patients with serious contrast allergy; whichever method is used should be used consistently.

Safety assessments will include adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Adverse events will be graded for severity per the National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE). Laboratory assessments, including serum chemistry, complete blood count (CBC), coagulation, urinalysis, and pregnancy tests, should be performed at a local certified laboratory. Details for hepatitis B and hepatitis C are listed in Section 5.8.5.

In addition, blood samples will be collected sparsely at predose and 2 hours (± 30 minutes) postdose on Day 1 of Cycle 1 and Cycle 2 to evaluate the exposure of zanubrutinib.

Tumor tissue must be sent to the central laboratory for CD79B mutation status analysis at the Prescreening Visit. For those patients enrolled, other predictive biomarkers will also be determined during screening and correlated with response, resistance, and prognosis. CD79B mutation status in the blood will be assessed. Blood-based biomarker analysis will also be performed to explore their association with response, resistance, and prognosis.

3.2. Study Schema

The study schematic is provided in Figure 1.

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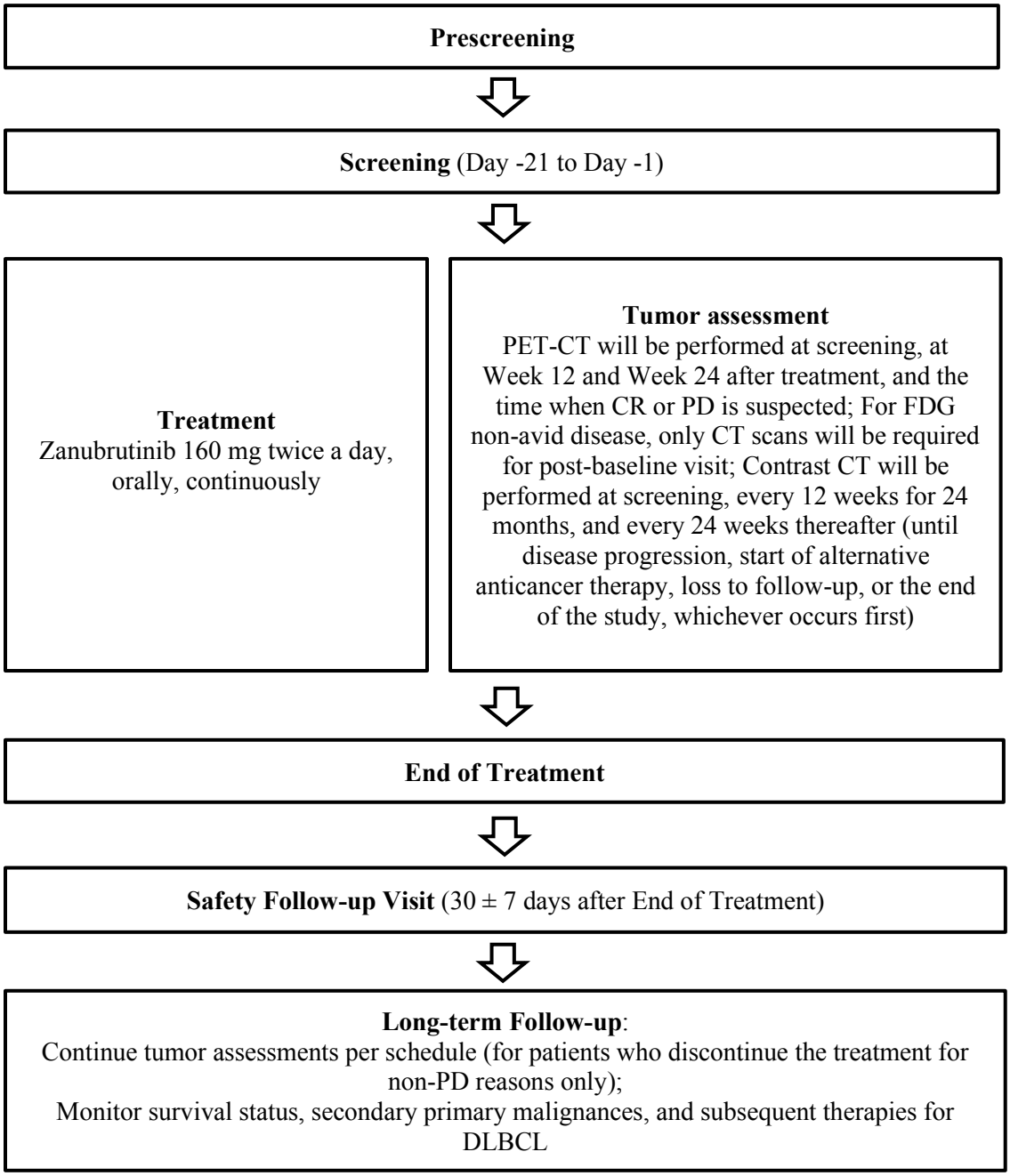
Figure 1: Study Schema



Abbreviations: CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; PET, positron emission tomography.

3.3. Blinding

Treatment with zanubrutinib will be open label.

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. No eligibility waivers will be granted.

4.1. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of informed consent.
2. Histologically confirmed DLBCL based on the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissue.
3. Positive CD79B mutation confirmed by the central laboratory.
4. Previously received at least 1 line of adequate systemic anti-DLBCL therapy, defined as an anti-CD20 antibody-based chemoimmunotherapy for at least 2 consecutive cycles, unless patients had disease progression before Cycle 2.
5. Relapsed or refractory (R/R) disease before study entry, defined as either:
   a. Recurrent disease after having achieved disease remission (CR or partial response [PR]) at the completion of the latest treatment regimen.
   b. Stable disease or PD at the completion of the latest treatment regimen.
6. Ineligible for high dose therapy/stem cell transplantation, which is defined as meeting any of the following criteria:
   a. Significant organ dysfunction (eg, left ventricular ejection fraction < 50% by echocardiogram or multiple gated acquisition scan [MUGA], diffuse lung capacity for carbon monoxide < 60% predicted by pulmonary function test, creatinine clearance < 70 mL/min shown by nuclear medicine scan or 24-hour urine collection) or comorbidities precluding the use of high dose therapy/stem cell transplantation on the basis of unacceptable risk of treatment-related morbidity.
   b. Failure to achieve CR or PR with salvage therapy.
   c. Failure to collect stem cells or unable to perform stem cell collection as assessed by the investigator.
7. Patients who have completed autologous stem cell transplantation ≥ 100 days before the first dose of zanubrutinib may be enrolled.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
9. Measurable disease as defined by at least 1 lymph node > 1.5 cm in longest diameter, or at least 1 extranodal lesion that is > 1.0 cm in longest diameter.
10. Adequate hematologic function, defined as:
    a. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L, except for patients with bone marrow involvement in which ANC must be ≥ 0.75 x 10^9/L, independent of growth factor support within 7 days before the first dose of study drug.

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b. Platelet count ≥ 75 x 10^9/L (or ≥ 50 x 10^9/L for patients with bone marrow involvement of lymphoma), independent of growth factor support or transfusion within 7 days before the first dose of study drug.
c. Hemoglobin > 80 g/L, independent of growth factor support or transfusion within 7 days before the first dose of study drug.

11. Adequate hepatic function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN).
    b. Total bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome, in which case ≤ 5 x ULN is allowed).
12. Adequate renal function, defined as creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]).
13. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN.
14. Female patients of childbearing potential must practice highly effective methods of contraception (Section 5.3) starting from before the first dose of study drug, throughout the study treatment, and for up to 1 month after the last dose of zanubrutinib.
15. Male patients are eligible if abstinent or vasectomized or if they agree to use highly effective contraception (as described in Section 5.3) during the study treatment period and for up to 1 week after the last dose of zanubrutinib.
16. Life expectancy of > 3 months.
17. Able to provide written informed consent and can understand and comply with the requirements of the study.

4.2. Exclusion Criteria

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

1. Patients who have NHL other than classical histology DLBCL (DLBCL, not otherwise specified), eg, patients with DLBCL transformed from indolent lymphomas, primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, primary effusion lymphoma, and central nervous system (CNS) lymphoma.
2. History of allogeneic stem cell transplantation or chimeric antigen receptor (CAR) T-cell therapy.
3. Prior exposure to a BTK inhibitor.
4. Receipt of the following treatment at the time indicated before the first dose of study drug:
    a. Corticosteroid given with antineoplastic intent within 2 weeks, but a short course (≤ 7 days) of systemic corticosteroid treatment at doses ≤ 20 mg/day prednisone

equivalent for control of lymphoma-related symptoms is allowed prior to enrollment provided that it is tapered off within 5 days after initiation of study treatment.
   b. Chemotherapy or radiotherapy within 2 weeks.
   c. Monoclonal antibody within 2 weeks.
   d. Investigational therapy within 2 weeks.
   e. Chinese patent medicine with antineoplastic intent within 2 weeks.

5. Toxicity of Grade ≥ 2 from prior anticancer therapy (except for alopecia, ANC, hemoglobin and platelets. For ANC, hemoglobin and platelets, please follow inclusion criterion #10).
6. History of other active malignancies within 2 years before study entry, with the exception of (1) adequately treated in-situ carcinoma of the cervix; (2) localized basal cell or squamous cell carcinoma of the skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
7. Clinically significant cardiovascular disease including the following:
   a. Myocardial infarction within 6 months before screening.
   b. Unstable angina within 3 months before screening.
   c. Clinically significant arrhythmia (eg, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes).
   d. QTcF (Fridericia's correction) > 480 msec.
   e. History of second-degree atrioventricular (AV) block Type II or third-degree AV block.
   f. New York Heart Association class 3 or 4 congestive heart failure (see Appendix 3).
   g. Uncontrolled hypertension as indicated by at least 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening.
8. 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.
9. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
10. Inability to swallow capsules or presence of a disease that significantly affects gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
11. Active fungal, bacterial and/or viral infection that requires systemic therapy.
12. Known HIV, or serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as follows:
   a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but without HBsAg, are eligible if HBV DNA is undetectable (< 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.

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b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (< 15 IU/mL).

13. Requires ongoing treatment with strong and moderate CYP3A inhibitors or inducers (see Appendix 4). If patients have been on strong or moderate CYP3A inhibitors or inducers in the past, they will not be eligible if the administration was within 7 days (or 5 half-lives of these drugs) before the first dose of study drug.
14. Major surgery within 4 weeks before the first dose of study drug.
15. Live vaccination within 4 weeks before the first dose of study drug.
16. Any medical condition or organ system dysfunction that, in the investigator's opinion, could compromise the patient's safety or put the study at risk.
17. Pregnant or lactating women.

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5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 1).

5.1. Visit Windows

The schedule of visits and assessments will be fixed from Cycle 1 Day 1 in this study. The study visit schedule is based around 28-day cycles. Acceptable windows around these visits are indicated in Appendix 1. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2. Informed Consent

A separate prescreening informed consent form must be signed before prescreening evaluation to obtain tissues for CD79B mutation test. At the Prescreening and Screening Visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the ICF will be given to the patient to read, and the patient must have adequate time to understand the content and ask questions.

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care. Personnel must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 21-day screening period. Consent must be obtained using the most current version of the form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

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

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

5.3. Females of Childbearing Potential and Contraception

Female patients of childbearing potential must practice highly effective methods of contraception starting from before the first dose of study drug, throughout the study treatment, and for up to 1 month after the last dose of zanubrutinib. A woman is considered to be of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Highly effective contraceptive methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal

- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day before the first dose of study drug, throughout the study treatment, and for up to 1 month after the last dose of zanubrutinib for female patients and up to 1 week after the last dose of zanubrutinib for male patients). 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.

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

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

Male patients are eligible if abstinent (as defined above) or vasectomized or if they agree to use of barrier contraception in combination with other methods described above during the study treatment period and for up to 1 week after the last dose of zanubrutinib.

5.4. Enrollment

5.4.1. Prescreening

Prescreening evaluations of CD79B mutation status will be performed for the patients who have histologically confirmed DLBCL and show the trend of lack of efficacy in their current systemic anti-DLBCL treatments, or the trend of disease progression. Definitions of the trend of lack of efficacy, or the trend of disease progression are as followed:

- Patients failed to achieve PR or better after at least 2 consecutive cycles of the current systemic anti-DLBCL therapy, or

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- Patients whose disease lesions enlarged, or new lesions appeared, which were suspected of disease progression by investigators.

Tumor tissue will be collected and sent to the central laboratory for CD79B mutation confirmation. A separate prescreening informed consent form must be signed to obtain tissue. Any AE or SAE evaluated by the investigators as related to the procedures for study-relevant tumor tissue collection (eg, biopsy) after signing the prescreening informed consent form should be recorded in the electronic case report form (eCRF).

For DLBCL patients who were CD79B mutant tested by local laboratories, they should provide the reports to the sponsor for review and approval to start the screening evaluations, without waiting for the central laboratory confirmation result. Meanwhile, tumor tissues are still required for confirmation of CD79B mutation status at central laboratory.

Only DLBCL patients with centrally confirmed CD79B mutation (except for patients with CD79B mutation locally confirmed and approved by the sponsor) and refractory or relapsed disease as confirmed by investigators are eligible for screening evaluations.

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5.4.2. Screening

All screening procedures must be performed within 21 days before the first dose of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. The investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

5.4.3. 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 numbers will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

5.4.4. Medical and Cancer History

Medical and cancer history, including presence or absence of disease-related constitutional symptoms, will be reviewed any time after informed consent has been obtained. Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) that do not pertain to the study indication, that started before signing of the informed consent, and that are considered relevant for the patient's study eligibility will be collected and captured in the eCRF. "Clinically significant" is defined as any event, diagnosis or laboratory value that requires treatment or follow-up or if there if in 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 date of initial diagnosis and current disease status), staging, and sites of disease, will also be collected. Prior medications/significant nondrug therapies and demographic data (gender, year 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

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conditions diagnosed within the previous 10 years that are considered clinically significant by the investigator. Significant findings that were present before signing of the informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF.

5.4.5. Confirmation of Eligibility

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

The archival tissue sample used for DLBCL diagnosis or the associated pathology report from diagnosis will be sent to the central pathology laboratory for confirmation of tissue diagnosis retrospectively. The status of CD79B should be confirmed by the central laboratory. Refer to Section 5.10 for more details.

5.5. Zanubrutinib Dispensation

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

5.6. Safety Assessments

5.6.1. Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), and weight will be performed at the Screening Visit, each visit during study treatment, and the Safety Follow-up Visit. Height (cm) is determined at screening only.

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

A complete physical examination is performed at the study site and includes an assessment of systems per standard of care and as clinically indicated by symptoms. 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. To the extent feasible, blood pressure will be measured using the same arm throughout the study. Patients must be resting in a sitting position for 10 minutes before vital signs are obtained. If blood pressure is > 150/100 mm Hg in a patient without a history of

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hypertension or is increased by > 20 mm Hg (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 and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured.

5.6.2. ECOG Performance Status

ECOG performance status will be assessed at the Screening Visit, each visit during study treatment, and the Safety Follow-up Visit.

5.6.3. Electrocardiogram

A 12-lead ECG will be performed locally in triplicate (≥ 1 minute apart) at screening for all patients and as clinically indicated at other timepoints. The calculated QTcF average of 3 ECGs must be ≤ 480 msec for eligibility. Patients should in a supine position and resting for at least 10 minutes before the ECG is obtained.

5.6.4. Echocardiogram/Multiple Gated Acquisition Scan

An echocardiogram or MUGA is to be performed at screening unless one has been performed within 30 days before the first dose of study drug.

5.6.5. Pulmonary Function Test

Pulmonary function will be assessed at screening and as clinically indicated during the study.

5.6.6. Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 21 days before the first dose of study drug, and on study thereafter until 30 days after the last dose of zanubrutinib.

5.6.7. Adverse Events Review

Adverse events that occurred during prescreening or screening will be recorded on the medical history case report form and in the patient's source document. For prescreening, only AEs or SAEs evaluated by the investigator as related to the procedures for study-relevant tumor tissue collection (eg, biopsy) after signing the prescreening informed consent form should be recorded.

The adverse event reporting period is defined in Section 8.4.1.

The accepted regulatory definition for an adverse event is provided in Section 8.1.1 and the definition of an serious adverse event is provided in Section 8.2. Important additional requirements for reporting serious adverse events are explained in Section 8.

5.7. Efficacy Assessments

Treatment response will be assessed by the investigator according to the Lugano classification for NHL (Cheson et al 2014). The primary endpoint will be the overall response rate based on the investigator assessment. Response parameters will include assessment of lymphadenopathy, hepatomegaly and splenomegaly, and bone marrow aspirate and biopsy. In the event of a

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treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 1).

5.7.1. Radiographic Imaging

All patients must have a baseline PET-CT and CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated (within 21days before the first dose of study drug).

PET-CT scans are required at screening, at Week 12 and Week 24 after treatment, and at the time when CR or PD is suspected. For FDG non-avid disease, only CT scans will be required for post-baseline visit. Contrast CT will be performed at screening, every 12 weeks for 24 months, and every 24 weeks thereafter until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first. 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. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of PET-CT shall prevail.

MRI and a non-contrast chest CT scan may be used instead of contrast CT for patients with serious contrast allergy; whichever method is used should be used consistently. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is constant throughout a patient's course on study.

Clinical suspicion of disease progression at any time will require radiologic confirmation to be performed promptly, rather than waiting for the next scheduled radiologic assessment.

5.7.2. Bone Marrow Examination

Bone marrow biopsy and aspirate are required to assess bone marrow involvement of lymphoma for all patients during the screening period, unless they have been performed within 60 days before the first dose of study drug as part of the standard care and there has been no intervening therapy from the time of the biopsy/aspirate until the start of study drug. For patients with bone marrow involvement of lymphoma at baseline, repeated bone marrow biopsy and aspirate are required if CR is suspected.

Bone marrow aspirates will be reviewed by local laboratory and results will be entered into the eCRF. In addition, all the bone marrow biopsies from screening to end of study will be collected to be reviewed by a pathologist from central pathology laboratory.

5.8. Laboratory Assessments

Laboratory assessments should be performed at a local certified laboratory, except for hepatitis B and hepatitis C testing of some cases; please refer to Section 5.8.5.

Serum chemistry, CBC, coagulation, urinalysis, and hepatitis serologies testing will be performed at the timepoints specified in the Schedule of Assessments (Appendix 1) and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first dose of study drug.

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Abnormal laboratory values will constitute adverse events only if they are associated with clinical signs or symptoms that are clinically significant and/or require therapy, and should be recorded in the adverse events eCRF. In addition, isolated abnormal laboratory values that are considered clinically significant (eg, the value causes study discontinuation or constitutes in and of itself a serious adverse event) should be recorded in the adverse events eCRF.

5.8.1. Hematology

CBC with differential is required to be performed at screening (a repeated CBC test is required if not done within 7 days before the first dose of study drug), and at every visit during the treatment phase and the Safety Follow-up Visit. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell (WBC) count with differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

5.8.2. Serum Chemistry

Serum chemistry testing includes sodium, potassium, chloride, uric acid, bicarbonate/total carbon dioxide, glucose, urea or blood urea nitrogen (BUN), creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, LDH, and alkaline phosphatase and is required to be performed at screening, every visit during the treatment phase, and at the Safety Follow-up Visit.

5.8.3. Coagulation

The coagulation profile includes prothrombin time (which will also be reported as international normalized ratio [INR]) and activated partial thromboplastin time (aPTT). The coagulation profile will be performed at screening, on Day 1 of subsequent cycles, and at the Safety Follow-up Visit.

5.8.4. Urinalysis

Urinalysis (which includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose) will be performed at screening.

5.8.5. Hepatitis B and C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. Viral hepatitis B and C testing may be performed by a local laboratory if the laboratory is able to perform the test to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C, respectively); otherwise the results must be confirmed by the central laboratory. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as HBV DNA by polymerase chain reaction (PCR) if the patient is negative for HBsAg but is HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

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Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo at least monthly (± 7 days) HBV DNA screening by PCR. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antiviral therapy, HBV DNA screening by PCR must be done at least every 90 days (± 7 days).

During monthly monitoring of HBV DNA by PCR, if the value is between 20 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drug should be stopped and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped and antiviral therapy initiated or continued. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with and approved by the medical monitor and physicians with expertise in managing hepatitis B.

Patients who are positive for HCV antibody but negative for HCV RNA must undergo monthly (± 7 days) HCV RNA screening. Patients with HCV RNA of 15 IU/mL or greater should stop study drug, and antiviral therapy should be initiated. The question of whether to resume study drug in patients whose HCV reactivation resolves should be discussed with and approved by the medical monitor and physicians with expertise in managing hepatitis C.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation. Table 2 describes how the results for HBV and HCV testing at screening relate to study eligibility.

Table 2: Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) and HBcAb (+) HBV DNA "Not detected" Perform monthly (± 7 days) monitoring of HBV DNA (or at least every 90 ± 7 days for patients receiving prophylactic antiviral therapy)	HBsAg (-) and HBcAb (+) HBV DNA detected
HCV	Antibody (-) or Antibody (+) HCV RNA "Not detected" Perform monthly (± 7 days) monitoring of HCV RNA	Antibody (+) HCV RNA Detected

Abbreviations: DNA, deoxyribonucleic acid; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; RNA, ribonucleic acid.
Note: All samples will be detected by polymerase chain reaction (PCR). For HBV DNA, detected means HBV DNA ≥ 20 IU/mL, and undetected means HBV DNA < 20 IU/mL; for HCV RNA, detected means HCV RNA ≥ 15 IU/mL, and undetected means HCV RNA < 15 IU/mL.

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5.8.6. Pregnancy Test

For women of childbearing potential, a serum pregnancy test will be performed at screening and at the end of treatment. Patients must have a negative serum pregnancy test at screening. Pregnancy tests must be performed at each visit during the treatment period and at the Safety Follow-up Visit. Any patient who is pregnant will not be eligible for the study. Subsequent tests at each visit may be urine tests, and if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after initiation of study treatment will be immediately withdrawn from participation in the study.

5.9. Pharmacokinetics

Blood samples will be collected sparsely at predose and 2 hours (± 30 minutes) postdose on Day 1 of Cycle 1 and Cycle 2 to evaluate the exposure of zanubrutinib. The actual collection date and time of each blood sample will be recorded in the eCRF. In addition, patients will be instructed to record the dosing time of the evening dose at home (and be recorded on the eCRF) prior to coming in for the predose sample on Day 1 of Cycle 2. Additional PK samples may be taken if needed.

Blood samples for PK analysis will be collected into ethylenediaminetetraacetic acid (EDTA) collection tubes. Shipping, storage, and handling of samples will be managed through a central laboratory. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual. Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma zanubrutinib concentrations using a validated method.

5.10. Biomarker Assessments

Samples for biomarker assessment will be collected as specified in the Schedule of Assessments (Appendix 1). Shipping, storage, and handling of the samples for biomarker assessments will be managed through a central laboratory. Refer to the laboratory manual for details about sample handling.

Approximately 10 unstained slides must be sent to the central laboratory for detection of CD79B mutation status at the Prescreening Visit. A fresh tumor biopsy is preferred at prescreening. If fresh tumor biopsies are not available, then an archival tumor tissue taken within 2 years before prescreening will be requested. Prescreening of a patient who cannot provide sufficient tumor tissue or biopsy may be permitted on a case-by-case basis after discussion with the medical monitor and in consultation with the sponsor.

For patients who proceed to screening stage, 5 more unstained slides should be sent to the central laboratory for analysis of other potential predictors of response including assessment of subtypes, MYD88L265P mutation, and BCL2/MYC/TCL1A expression. DLBCL characteristic markers may also be assessed. Residual samples from prescreening may be allowed to be used for the related exploratory biomarker testing. Enrollment of a patient who cannot provide sufficient tumor tissue may be permitted on a case-by-case basis after discussion with the medical monitor and in consultation with the sponsor.

Optional biopsy will also be taken during the study from accessible tumor sites in patients who have confirmed disease progression; these biopsies are done to explore genetic alterations

associated with drug resistance, including DNA alterations and analyses of the subtype (based on the gene expression profile). Written patient consent is required for fresh tumor biopsies.

For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood samples will be collected at screening, time of first response, and time of disease progression. CD79B mutation status in blood will be assessed. Blood-based biomarker analysis such as DNA/ctDNA alterations will be performed to explore their association with response, resistance, and prognosis.

5.11. Unscheduled Visits

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

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

5.12. End of Treatment

The treatment period starts with the first day of assigned study treatment and continues until the last dose of study drug has been administered.

Study drug will be discontinued for any of the following reasons:

- Disease progression
- Any intolerable adverse event that cannot be improved with standard medical intervention or that would lead to undue risk to the patient
- Consent withdrawal by the patient
- Patient pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Other

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

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5.13. Safety Follow-Up Visit

All patients who permanently discontinue study drug will have a Safety Follow-up Visit approximately 30 days (± 7 days) after the last dose of zanubrutinib. Refer to the Schedule of Assessments (Appendix 1) for the assessments to be performed at the Safety Follow-up Visit.

Adverse events need to be collected at the Safety Follow-up Visit, including those that may have occurred or have been ongoing after the patient discontinued study treatment. All adverse events, including serious adverse events, will be collected as described in Section 8. The adverse event reporting period is defined in Section 8.4.1.

The investigator or his/her designee will also continue to collect information on alternative anticancer therapy given after the last dose of study drug. A laboratory assessment is required only if at the previous visit the patient had an ongoing laboratory abnormality that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information.

5.14. Long-Term Follow-Up

All patients who discontinue study drug treatment will remain in the study, complete the Safety Follow-up Visit, and subsequently commence long-term follow-up, which includes monitoring for survival status, second primary malignances, subsequent therapies for DLBCL, and may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic progression. Visits repeat every 12 weeks (± 14 days) until the end of the study. For patients who permanently discontinue study drug treatment before radiographic progression is documented and confirmed by the investigator, tumor assessments will continue until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first.

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

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5.15. End of Study

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

- Consent withdrawal by the patient
- Death
- Study termination by sponsor
- Other

Patients may voluntarily withdraw consent for the study at any time. The overall study ends when the primary analysis takes place.

At the end of the study as determined by the sponsor, any patient who is still on treatment and continues to benefit from study drug, in the opinion of the investigator, may be offered the option of continued access.

5.16. Loss to Follow-Up

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

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

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

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6. STUDY TREATMENT

6.1. Zanubrutinib

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

6.1.1. Packaging and Labeling of Zanubrutinib

Zanubrutinib capsules will be provided in a child-resistant, high-density, polyethylene bottle with induction seal and bottle label. Labels will be prepared in accordance with local regulatory guidelines of each country participating in the study. Label text will be translated into local language as required. The contents of the study treatment labels will be in accordance with all applicable local regulatory requirements.

6.1.2. Handling and Storage of Zanubrutinib

The Interactive Response Technology (IRT) system will be used for drug supply management. The study drugs will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. Zanubrutinib bottles must be stored at room temperature 15ºC to 30ºC (59°F to 86°F). Do not use beyond the expiration date stamped on the label.

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

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

6.1.3. Compliance and Accountability of Zanubrutinib

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

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

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6.1.4. Disposal and Destruction of Zanubrutinib

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

6.1.5. Dosage and Administration of Zanubrutinib

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at approximately the same time each day of dosing. Patients will be asked to complete a patient diary that records dates and times of dosing between clinic visits. Patients will be requested to bring their diaries, unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded in the appropriate eCRF.

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

If a dose of the study drug is not taken at the scheduled time, the patient should skip the study drug if the time to next dose is 8 hours or less and return to normal dosing with next dose. If a patient vomits after taking the zanubrutinib capsules, that dose should not be repeated.

6.1.6. Precautions of Zanubrutinib

6.1.6.1. Overdose

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

6.1.6.2. Surgery and Procedures

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

6.1.7. Dose Interruption and Modification of Zanubrutinib

The guidelines shown in Table 3 should be followed for dose interruption or modification of zanubrutinib for hematologic toxicities (Section 6.1.7.1) or nonhematologic toxicities (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events;

laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) (Section 6.1.7.2).

Table 3: Zanubrutinib Dose Reduction Levels

Toxicity Occurrence	Dose Level	Zanubrutinib Dose
First	0 = starting dose	Restart at 160 mg twice daily
Second	-1 dose level	Restart at 80 mg twice daily
Third	-2 dose level	Restart at 80 mg once daily
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

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

6.1.7.1. Zanubrutinib Dose Reductions for Hematologic Toxicity

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

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

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

If the same event reoccurs, treatment will be restarted at 1 dose level lower (level -1) after the toxicity has recovered 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 discussed with the medical monitor.

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

Any hematologic toxicities beyond the above-mentioned conditions determined by investigators as requiring Zanubrutinib dose interruptions or reductions need to be discussed with the medical monitor.

6.1.7.2. Zanubrutinib Dose Reductions for Nonhematologic Toxicity

Zanubrutinib should be withheld for any ≥ Grade 3 hemorrhage. The drug should be permanently discontinued for any treatment-related ≥ Grade 3 hemorrhage unless the underlying condition can be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of

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rebleeding is deemed acceptable. Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

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

Any nonhematologic toxicities beyond the above-mentioned conditions determined by the investigators as requiring Zanubrutinib dose interruptions or reductions need to be discussed with the medical monitor.

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

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7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

Medications taken within 4 weeks before the first dose and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, will be recorded in the eCRF and in the patient's source documents. If any AE or SAE is reported during the prescreening phase, related medications should also be recorded in the eCRF.

All prior therapies for DLBCL, including immunochemotherapy, chemotherapy, transplant, targeted therapy, radiation therapy, etc, will be recorded in the eCRF with the start and end dates of administration.

Per the study eligibility criteria, patients who received certain prior medications and therapies for DLBCL (including prior allogeneic hematopoietic stem cell transplantation and prior exposure to a BTK inhibitor) are excluded from study participation.

7.2. Concomitant Therapy

All concomitant medications taken during the study (from enrollment until 30 days after the last dose of zanubrutinib) will be recorded in the eCRF with indication, dose information, and dates of administration.

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

7.2.1. Permitted Medications

The following treatments are allowed:

- Blood product transfusion and growth factor support per standard of care and institutional guidelines.
- Corticosteroids for non-NHL indication(s).
  - Patients should not receive treatment with systemic corticosteroid other than intermittently to control or prevent infusion reactions or for short durations (< 2 weeks) to treat non-NHL-related condition(s) (eg, to treat a flare of chronic obstructive pulmonary disease).
  - A short course (≤ 7 days) of systemic corticosteroid treatment at doses ≤ 20 mg/day prednisone equivalent for control of lymphoma-related symptoms is allowed prior to enrollment provided it is tapered off within 5 days after initiation of study treatment.
  - Chronic systemic corticosteroid use is not permitted, except for adrenal replacement, which requires consultation with the medical monitor.
- Therapy to reduce symptoms per standard of care and institutional guidelines.

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

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

7.2.2. Prohibited Medications

Patients should not receive other anticancer therapy (eg, chemotherapy, radiotherapy, biologics, or immunotherapy) while on treatment in this study. Vaccination with live virus vaccines is not allowed within 4 weeks before the first dose of study drug or during treatment.

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 4 for a list of these medications), grapefruit juice, and Seville oranges should be done with caution, as these may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification guidance in Table 4. The medical monitor and clinical pharmacologist should be consulted in these situations. Please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers List (FDA 2019) for a more complete list.

Clinical drug-drug interaction studies 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, because zanubrutinib may decrease the plasma exposures of these drugs.

Since blood levels and efficacy 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, use of a second barrier method of contraception (eg, condoms) is recommended. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution because zanubrutinib may increase their concentrations.

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Table 4: Dose Modification for Zanubrutinib When Coadministered With Strong/Moderate CYP3A Inhibitors or Inducers

Coadministered Drug	Recommended Zanubrutinib Dose
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions (Section 6.1.7)
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions (Section 6.1.7)
Moderate or strong CYP3A inducer	Avoid concomitant use

Abbreviation: CYP, cytochrome P450.

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8. SAFETY MONITORING AND REPORTING

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

8.1. Adverse Events

8.1.1. Definitions and Reporting of an Adverse Event

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

Examples of an adverse event include:

- Worsening of a chronic or intermittent preexisting condition including an increase in severity, frequency, or duration, and/or that is associated with a significantly worse outcome.
- New condition(s) detected or diagnosed after study drug administration even if 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 (an overdose itself should not be reported as an adverse event or serious adverse event).

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

8.1.1.1. Assessment of Severity

The investigator will assess the severity for each adverse event and serious adverse event reported during the study. When applicable, adverse events and serious adverse events should be assessed and graded based upon the NCI-CTCAE Version 5.0.

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

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- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to adverse event

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

8.1.1.2. Assessment of Causality

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

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

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

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- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the adverse event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the adverse event (eg, the patient's clinical condition or other concomitant adverse events).

8.1.1.3. Following Adverse Events and Serious Adverse Events

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

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

All adverse events and serious adverse events will be followed until resolution, the condition stabilizes or is considered chronic, the adverse event or serious adverse event is otherwise explained, the patient is lost to follow-up, the patient withdraws consent, or the initiation of any alternative anticancer therapy, whichever comes first. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the adverse event or serious adverse event. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

New or updated information should be reported to the sponsor according to the serious adverse event instructions provided to the site within the time frames outlined in Section 8.6.1.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, echocardiogram/MUGA, pulmonary function test, or vital signs) that are judged by the investigator as clinically significant will be recorded as adverse events or serious adverse events. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worsen will not be reported as adverse events or serious adverse events. The definition of clinically significant is left to the judgment of the investigator. In general, these are laboratory test abnormalities that are associated with clinical signs or symptoms, or require active medical intervention, or lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or further diagnostic investigation.

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Asymptomatic treatment-related lymphocytosis should not be considered an adverse event.

8.2. Definition of a Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: the term "life-threatening" in the definition of "serious" refers to an adverse event in which the patient was at risk of death at the time of the adverse event; it does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

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

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
- Results in a congenital anomaly/birth defect
- Is considered a significant medical adverse event by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered serious adverse events:

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

8.3. Suspected Unexpected Serious Adverse Reaction

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

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

8.4.1. Adverse Event Reporting Period

After signing the prescreening informed consent form, any AE or SAE evaluated by the investigators as related to the procedures for study-relevant tumor tissue collection (eg, biopsy) should be reported.

After screening informed consent has been signed but before the administration of the study drug, only serious adverse events should be reported. If, after signing the informed consent but before the first dose of study drug, the patient experiences a new or worsening condition that does not meet the definition of serious, that condition should be reported only as medical history.

After initiation of study drug, all adverse events and serious adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of zanubrutinib or the initiation of any alternative anticancer therapy, whichever comes first. After this period, the investigator should only report any serious adverse events that are believed to be related to zanubrutinib.

8.4.2. Eliciting Adverse Events

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

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

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

8.5.1. Disease Progression

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

8.5.2. Death

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

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8.6. Reporting of Serious Adverse Events

8.6.1. Prompt Reporting of Serious Adverse Events

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

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

	Timeframe for sending initial/follow-up report [a]	Documentation method	Reporting method
All SAEs	Within 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE form to safety portal [b]

Abbreviations: SAE, serious adverse event.

a Report follow-up information that is clinically relevant and pertaining to the serious adverse event, which includes but is not limited to the following: update to the serious adverse event, new additional serious adverse event, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to study drug(s). Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.

b Serious adverse event reports should be submitted to the sponsor safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper serious adverse event form should be submitted by email or fax.

8.6.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

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

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

8.7. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 30 days after the last dose of zanubrutinib, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Zanubrutinib (BGB-3111) Investigator's Brochure

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9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Study Endpoints

All the responses in the efficacy endpoints below are determined by investigator assessment according to the Lugano classification for NHL (Cheson et al 2014).

9.1.1. Primary Endpoint

- Overall response rate determined by the investigator assessment

9.1.2. Secondary Endpoints

- Efficacy endpoints of zanubrutinib therapy are as follows:
  - Complete response rate determined by investigator assessment
  - Duration of response determined by investigator assessment
  - Progression-free survival determined by investigator assessment
  - Time to response determined by investigator assessment
  - Overall survival
- Safety parameters, including adverse events and serious adverse events (per NCI-CTCAE Version 5.0), clinical laboratory measurements, physical examination, and vital signs

9.1.3. Exploratory Endpoints

- PK evaluations of zanubrutinib, including summary of plasma concentrations
- Clinical outcomes (eg, overall response rate, complete response rate, duration of response, progression-free survival, time to response, and overall survival) by clinical/genetic risk factors
- Potential resistance biomarkers and mechanisms of disease resistance

9.2. Statistical Analysis

9.2.1. Analysis Sets

Safety Analysis Set: includes all patients who receive at least one dose of zanubrutinib. The Safety Analysis Set will be used for both safety and efficacy analyses.

PK Analysis Set: includes all patients for whom there is at least one available postdose zanubrutinib PK concentration measurement.

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9.2.2. Patient Disposition

The number of patients screened, enrolled, treated, and discontinued from study drug or the study will be summarized. The primary reason for study drug discontinuation will be summarized according to the categories recorded in the eCRF. The end of study status (alive, death, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF. Major protocol deviations will be summarized and listed by each category.

9.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set using descriptive statistics. Continuous variables include but are not limited to age, weight, vital signs, time since initial DLBCL diagnosis; categorical variables including but not limited to sex, age group, disease stage, ECOG performance status, and prior line of therapy for DLBCL. Baseline bone marrow involvement and International Prognostic Index will also be summarized.

9.2.4. Prior and Concomitant Therapy

Prior medications will be defined as medications that stopped before the first dose of study drug.

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the last dose of zanubrutinib. Concomitant medications will be assigned a preferred name using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification.

Prior and concomitant medications will be summarized and listed by preferred name and therapeutic class.

9.2.5. Efficacy Analyses

Efficacy assessments will use the Lugano classification to assess overall disease response (see Appendix 2).

9.2.5.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the overall response rate determined by the investigator assessment, where the overall response rate is defined as the proportion of patients in the Safety Analysis Set whose best overall response is either CR or PR, and the best overall response is defined as the best response recorded from the start of zanubrutinib until the data cutoff date or the start of alternative anticancer treatment. Patients who drop out earlier with no post-baseline response assessment (for any reason) will be considered nonresponders for best overall response.

The overall response rate of historical control in this study is 30% based on the reported overall response rate in the literatures (Advani et al 2017; Assouline et al 2016; Budde et al 2018; Coiffier et al 2016; Czuczman et al 2017; Jurczak et al 2018; Hutchings et al 2018; Lesokhin et al 2016; Kalakonda et al 2020). Hence, the null and alternative hypotheses are set as follows:

H_0: overall response rate = 30%

H_a: overall response rate > 30%

A binomial exact test will be performed for hypothesis testing H_0 versus H_a in the Safety Analysis Set, and the overall type I error rate will be controlled at 1-sided significance level of 0.025. The primary analysis will take place approximately 6 months after the first dose of the last patient, as specified in Section 9.6. If the null hypothesis can be rejected in primary analysis at significance level of 0.025, it will be concluded that the historical control of 30% can be ruled out. A 2-sided Clopper-Pearson 95% CI of the overall response rate will also be calculated to assess the precision of the estimation.

Justification of historical control

At present, no related studies are designed based on BTK inhibitors in the population of R/R DLBCL with CD79B mutation. The overall response rate of historical control in this study is chosen based on the reported overall response rate in the literatures (Advani et al 2017; Assouline et al 2016; Budde et al 2018; Coiffier et al 2016; Czuczman et al 2017; Jurczak et al 2018; Hutchings et al 2018; Lesokhin et al 2016; Kalakonda et al 2020). It is reported that the overall response rates in patients with DLBCL treated by chemo-free therapy without BTK inhibitors are less than or approximately 30%, except that an overall response rate of 36% is reported in a study with a small sample size of 11 patients (Lesokhin et al 2016). Considering that DLBCL patients with CD79B mutation, compared with those without CD79B mutations, are associated with worse prognosis and shorter survival after standard treatment, the historical control is chosen to be 30%.

9.2.5.2. Secondary Efficacy Endpoint Analyses

Complete Response Rate by Investigator Assessment

The complete response rate will be determined by the investigator, and it is defined as the proportion of patients in the Safety Analysis Set whose best overall response is CR. The complete response rates along with their 95% CIs, using Clopper-Pearson method, will be provided.

Duration of Response by Investigator Assessment

The duration of response is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. The duration of response will be only summarized for responders. Censoring rules for duration of response followed progression-free survival censoring rules. The Kaplan-Meier method will be used to estimate duration of response curves and corresponding quantiles (including the median) (Schemper and Smith 1996). A 2-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The duration of response event-free rates at 6 and 12 months will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula (Kalbfleisch and Prentice 1980).

Progression-Free Survival by Investigator Assessment

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Progression-free survival is defined as the time from the starting date of the therapy to the date of first documentation of disease progression or death, whichever occurs first. Patients who do not have disease progression will be censored at their last valid response assessment.

The progression-free survival will be analyzed in a similar fashion as duration of response. The Kaplan-Meier method will be used to estimate progression event-free curves and corresponding quantiles (including the median) (Schemper and Smith 1996). A 2-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The progression-free survival probability at 6 and 12 months, defined as the percentages of patients in the analysis set who remain alive and progression-free at the specified timepoints, will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula (Kalbfleisch and Prentice 1980).

The progression-free survival censoring rule will follow FDA Guidance for Industry Clinical Study Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

Time to Response by Investigator Assessment

Time to response is defined as time from the starting date of the therapy to the date the response criteria are first met. Time to response will be summarized using sample statistics, such as sample mean, median, and standard deviation.

Overall Survival

Overall survival is defined as the time from the starting date of the therapy to the date of death due to any reason. Patients who are known to be alive as of their last known status will be censored at their date of last contact. The overall survival will be analyzed similarly as progression-free survival.

Additional details will be provided in the Statistical Analysis Plan.

9.2.6. Biomarker Analyses

The biomarker-related analysis will be provided in a separate report.

9.2.7. Pharmacokinetic Analyses

Plasma zanubrutinib concentration data collected sparsely at predose and 2 hours (± 30 minutes) postdose on Day 1 of Cycle 1 and Cycle 2 will be tabulated and summarized by cycle. Descriptive statistics including means, standard deviations, medians, and ranges as appropriate, will be used for the analysis of plasma zanubrutinib concentrations.

Additional analyses such as population PK analysis may be performed together with data from other studies, and the results from such analysis will be reported separately from the Clinical Study Report.

9.2.8. Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups, including but not limited to sex, age group, disease stage at study entry, disease status, ECOG performance status, number of prior lines of therapy, International Prognostic

Index, and bulky disease. Within group values (rates or means/medians) and CIs will be presented in forest plots.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all adverse events graded by NCI-CTCAE Version 5.0. Laboratory values (CBC, serum chemistry, coagulation and urinalysis), vital signs, physical exams, ECG, echocardiogram/MUGA, and pulmonary function test findings will also be used in assessing safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose reductions, dose interruption, and drug discontinuation due to adverse events will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized.

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

9.3.2. Adverse Events

The adverse event verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology defined by the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lowest level term that most closely resembled the verbatim adverse event term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event is defined as an adverse event that had an onset date or worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib, or the initiation of any alternative anticancer therapy, whichever comes first. Worsening of an event to Grade 5 beyond Day 30 after last dose of study drug of a treatment-emergent adverse event is also considered a treatment-emergent adverse event. Treatment-related adverse events include those adverse events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

Only those adverse events that were treatment-emergent will be included in summary tables. All adverse events, treatment-emergent or otherwise, will be presented in patient data listings. The incidence of treatment-emergent adverse events will be reported as the number (and percentage) of patients with treatment-emergent adverse events by SOC and PT. A patient will be counted only once by the highest severity grade according to NCI-CTCAE Version 5.0 within a SOC and PT, even if the patient experienced more than 1 treatment-emergent adverse event within a specific SOC and PT. The number (percentage) of patients with treatment-emergent adverse events will also be summarized by relationship to the study drug. The patient incidence of serious adverse events, treatment-emergent adverse events of Grade 3 or higher, treatment-emergent adverse events leading to death, treatment-emergent adverse events leading

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to treatment discontinuation and dose modification (dose reduction or dose interruption), and all above treatment-related treatment-emergent adverse events will be summarized. Deaths and cause of deaths will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (ie, hematology, serum chemistry, coagulation, and qualitative urinalysis) values will be evaluated for each laboratory parameter by patient. 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. 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 postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE Version 5.0 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) and changes from baseline will be presented by visit.

9.3.5. Electrocardiogram

ECG assessments will be performed at the Screening Visit and as clinically indicated. Descriptive statistics for baseline ECG parameters will be presented.

9.3.6. Echocardiogram/Multiple Gated Acquisition Scan

Echocardiogram/MUGA assessments will be performed at the Screening Visit unless one has been performed within 30 days before the first dose of study drug. Descriptive statistics for baseline electrocardiogram/MUGA parameters will be presented.

9.3.7. Pulmonary Function Test

Pulmonary function assessments will be performed at the Screening Visit and as clinically indicated. Descriptive statistics for baseline pulmonary function parameters will be presented.

9.4. Sample Size Consideration

The sample size of the study is planned based on the level of precision of overall response rate estimate as well as the power of a hypothesis testing against a historical rate. The targeted overall response rate in this study is 50%, which is deemed a clinically meaningful improvement based on a historical control of 30%. Assuming a true overall response rate of 50% in the study population, 66 patients will provide 90% power to reject the null hypothesis of 30% ORR at the one-sided significance level of 0.025. The 95% Clopper-Pearson CI will be (37.4%, 62.6%) with a sample size of 66 patients, when the observed overall response rate is 50%. The historical

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control rate is obtained from referenced studies (Advani et al 2017; Assouline et al 2016; Budde et al 2018; Coiffier et al 2016; Czuczman et al 2017; Jurczak et al 2018; Hutchings et al 2018; Lesokhin et al 2016; Kalakonda et al 2020).

9.5. Interim Analysis

No interim analysis is planned for this study.

9.6. Primary Analysis

The primary analysis will take place approximately 6 months after the first dose of the last patient. The null hypothesis H_0 is rejected if the p-value from an exact binomial test statistic is less than 0.025. Correspondingly, at least 28 responders are required in 66 patients.

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10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

No safety monitoring committee is planned in this study.

10.2. Provision of Study Results and Information to Investigators

When the Clinical Study Report is completed, the sponsor will provide the major findings of the study to the investigator.

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

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

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11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to 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 principles of the "Declaration of Helsinki," International Council on Harmonisation guidelines, the basic principles of "Good Clinical Practice" by National Medical Products Administration (NMPA) in April 2020, Section 4 "Investigators," and the basic principles of "Good Clinical Practice" as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56.

11.2.2. Ethical Conduct of the Study and Ethics Approval

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

The sponsor's sample ICF will be provided to each investigator who shall adapt it, subject to sponsor's approval, for use at his/her site. The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's ICF, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IRB/IEC. The IRB/IEC 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 IRB/IEC review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IRB/IEC approval, the approved ICF, and any other information that the IRB/IEC has approved for presentation to potential patients.

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

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11.2.3. Informed Consent

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

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

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

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

11.2.4. Investigator Reporting Requirements

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

11.2.5. Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

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- names or initials (full or partial);
- *full* dates of birth;
- contact information (such as phone numbers or home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

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

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain kinds of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, or on product dispensing logs provided to the sponsor, etc.).

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any

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third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

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11.2.6. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system in a timely manner.

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

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

11.2.7. Data Management/Coding

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

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

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

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

Adverse events will be coded using MedDRA. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

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11.2.8. Drug Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the EDC system will be assigned only to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC.

11.2.9. Drug Accountability

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

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

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

11.2.10. Inspections, Audits, and Monitoring Visits

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

11.2.11. Protocol Adherence

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

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

11.2.12. Financial Disclosure

Investigators and subinvestigators (as designated on the Form FDA1572) are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required, to the

appropriate health authorities. This is intended to ensure that financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, the last patient's last visit).

11.3. Protocol Modifications

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

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

11.4. Study Report and Publications

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2019).

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. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the

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terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

11.5. Study and Study Center Closure

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

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

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines that 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 IRB/IEC 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 return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

11.6. Records Retention and Study Files

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

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

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to)

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the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECGs, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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

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

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

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

Biological samples remaining after this study may be retained in storage by the sponsor for a period up to 10 years or as allowed by the IRB/IEC. A longer storage period may apply in the event that patients consent to BeiGene retaining remaining samples for future research.

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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.

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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 the following:

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

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

11.8. Joint Investigator/Sponsor Responsibilities

11.8.1. Access to Information for Monitoring

In accordance with International Council on Harmonisation Good Clinical Practices guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

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

11.8.2. Access to Information for Auditing or Inspections

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

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12. REFERENCES

Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol. 2013;31(1):88-94.

Advani RH, Lebovic D, Chen A, et al. Phase I study of the anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res. 2017;23(5):1167-76.

Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90(9):790-95.

Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503-11.

Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Patients Ineligible for or Having Failed Autologous Transplantation: A Single-Arm, Phase II Study. J Clin Oncol. 2019;37(6):JCO.18.00766.

Assouline SE, Nielsen TH, Yu S, et al. Phase 2 study of panobinostat with or without rituximab in relapsed diffuse large B-cell lymphoma. Blood. 2016;128(2):185-94.

Batlle-López A, González de Villambrosía S, Francisco M, et al. Stratifying diffuse large B-cell lymphoma patients treated with chemoimmunotherapy: GCB/non-GCB by immunohistochemistry is still a robust and feasible marker. Oncotarget. 2016;7(14):18036-49.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38(1):29-41.

Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol. 2018;15(1):31-46.

Budde LE, Sehn LH, Assouline S, et al. Mosunetuzumab, a full-length bispecific CD20/CD3 antibody, displays clinical activity in relapsed/refractory B-cell non-Hodgkin lymphoma (nhl): interim safety and efficacy results from a phase 1 study [Abstract 399]. Blood. 2018;(suppl 1):132.

Cameron F, Sanford M. Ibrutinib: First global approval. Drugs. 2014;74(2):263-71.

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31(11):1860-1.

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Carpio C, Bouabdallah R, Ysebaert L, et al. Avadomide monotherapy in relapsed/refractory DLBCL: Safety, efficacy, and a predictive gene classifier. Blood. 2020;135(13):996-1007.

Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-32.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol. 2014;32(27):3059-67.

Coiffier B. Diffuse large cell lymphoma. Curr Opin Oncol. 2001;13(5):325-34.

Coiffier B, Thieblemont C, de Guibert S, et al. A phase II, single-arm, multicentre study of coltuximab ravtansine (SAR3419) and rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. Br J Haematol. 2016;173(5):722-30.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.

Czuczman MS, Trněný M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res. 2017;23(15):4127-37.

Dal Porto JM, Gauld SB, Merrell KT, et al. B cell antigen receptor signaling 101. Mol Immunol. 2004;41(6-7):599-613.

Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature. 2010; 463(7277):88-92.

Dyer MJS, Vos SD, Ruan J, et al. Acalabrutinib monotherapy in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). J Clin Oncol. 2018;36(suppl 15):7547.

Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011(1):498-505.

Gazumyan A, Reichlin A, and Nussenzweig MC. Ig beta tyrosine residues contribute to the control of B cell receptor signaling by regulating receptor internalization. J Exp Med. 2006;203(7):1785-94.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.

Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer. 2011;117(22):5058-66.

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Humphries LA, Dangelmaier C, Sommer K, et al. Tec kinases mediate sustained calcium influx via site-specific tyrosine phosphorylation of the phospholipase Cgamma Src homology 2-Src homology 3 linker. J Biol Chem. 2004;279(36):37651-61.

Hutchings M, Iacoboni G, Morschhauser F, et al. CD20-Tcb (RG6026), a novel "2:1" format T-cell–engaging bispecific antibody, induces complete remissions in relapsed/refractory B-cell non-Hodgkin's lymphoma: preliminary results from a phase I first in human trial [Abstract 226]. Blood. 2018;(suppl 1):132.

International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2019. Available at: http://www.icmje.org/recommendations/. Accessed 15 March 2020.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Guideline for industry: E3 structure and content of clinical study reports. 1995.

Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Ann Oncol. 2018;29(5):1266-72.

Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020;7: e511-22.

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.

Kasamon YL, Price LSL, Okusanya OO, et al. FDA Approval Summary: Selinexor for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Oncologist. 2021;26(10):879-86.

Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol. 2016;34(23):2698-704.

Li XQ, Li GD, Gao ZF, et al. Distribution pattern of lymphoma subtypes in China: a nationwide multicenter study of 10002 cases. J Diagn. Concepts Pract. 2012;11(2):111-5.

Maerevoet M, Zijlstra JM, Follows G, et al. Survival among patients with relapsed/refractory diffuse large B cell lymphoma treated with single-agent selinexor in the SADAL study. J Hematol Oncol. 2021;14(1):111.

Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol. 2011;29(2):200-7.

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VV-CLIN-023261 Version 5.0

Moller MB, Pedersen NT, Christensen BE, et al. Diffuse large B-cell lymphoma: clinical implications of extranodal versus nodal presentation-a population-based study of 1575 cases. Br J Haematol. 2004;124(2):151-9.

National Cancer Institute (NCI). Common Toxicity Criteria, Cancer Therapy Evaluation Program. Version 5.0. 2017. Assessed 27 November 2017.

National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: B-cell lymphomas. Version 1.0. 2020. Accessed 22 January 2020.

Niiro H, Clark EA. Regulation of B-cell fate by antigen-receptor signals. Nat Rev Immunol. 2002;2(12): 945-56.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Petro JB, Khan WN. Phospholipase C-gamma 2 couples Bruton's tyrosine kinase to the NF kappaB signaling pathway in B lymphocytes. J Biol Chem. 2001;276(3):1715-9.

Reddy A, Zhang J, Davis NS, et al. Genetic and functional drivers of diffuse large B cell lymphoma. Cell. 2017;171(2):481-94.

Rickert RC. New insights into pre-BCR and BCR signalling with relevance to B cell malignancies. Nat Rev Immunol. 2013;13(8):578-91.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;7(4):343-6.

Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med. 2018;378(15):1396-407.

Shankland KR, Armitage JO, and Hancock BW. Non-Hodgkin lymphoma. Lancet. 2012;380(9844):848-57.

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993;329(14):987-94.

Surveillance Epidemiology and End Results (SEER), NCI, US National Institutes of Health, Fast Facts; Statistics Stratified by Cancer Site, 2010.

Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, BGB-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a phase 1 first-in-human trial. Blood. 2015;126:832.

Tam CS, Simpson D, Opat S, et al. Safety and activity of the highly specific BTK inhibitor zanubrutinib (BGB-3111) in patients with indolent and aggressive Non-Hodgkin’s Lymphoma.

Approved Date 6/6/2024
VV-CLIN-023261 Version 5.0

Oral presentation at: 61st American Society of Hematology Annual Meeting; 5-10 December 2019; Orlando, FL.

Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66(6):443-59.

Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. 2011;29(31):4079-87.

Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116-25.

US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). FDA guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2018.

US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). FDA guidance for industry: drug interaction studies – table of substrates, inhibitors and inducers. 2019.

Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922-6.

Witzig TE, Nowakowski GS, Habermann TM, et al. A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma. Ann Oncol. 2015;26(8):1667-77.

Xie Y, Pittaluga S, and Jaffe ES. The histological classification of diffuse large B-cell lymphomas. Semin Hematol. 2015;52(2):57-66.

Younes A, Ansell S, Fowler N, et al. The landscape of new drugs in lymphoma. Nat Rev Clin Oncol. 2017;14:335-46.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Phase or Visit	Prescreening	Screening	Treatment (1 Cycle = 28 days)						Safety Follow-Up Visit after End of Treatment[b]	Long-Term Follow-up[c]
			Zanubrutinib Monotherapy				Suspected			
Cycle/Period[a]			Cycle 1	Cycle 2	Cycle 3	Every 12 weeks after C4D1 through the end of Year 2, then every 24 weeks	CR	PD		
Day		-21 to -1	Day 1	Day 1	Day 1	Every 12 weeks or every 24 weeks as per above			30 days after End of Treatment[b]	Every 12 weeks
Window (Days)	–	–		± 7	± 7	± 7	–	–	± 7	± 14
Study Drug Administration										
Zanubrutinib (continuous)[d]	–	–	X	X	X	X				
Procedure										
Informed consent[e]	X	X								
Confirm eligibility[f]	X	X								
Medical & cancer history[g]		X								
CD79B mutant test[h]	X									
Biomarker tissue samples[i]		X						X		
Biomarker blood samples[j]		X	To be collected at the first time of response					X		
Safety Assessments[k]										
Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)[l]		X	X	X	X	X			X	
Physical examination[m]		X	X	X	X	X			X	
ECOG performance status		X	X	X	X	X			X	
ECHO/MUGA[n]		X								
12-lead ECG[o]		X								

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Study Phase or Visit	Prescreening	Screening	Treatment (1 Cycle = 28 days)						Safety Follow-Up Visit after End of Treatment[b]	Long-Term Follow-up[c]
			Zanubrutinib Monotherapy				Suspected			
Cycle/Period[a]			Cycle 1	Cycle 2	Cycle 3	Every 12 weeks after C4D1 through the end of Year 2, then every 24 weeks	CR	PD		
Day		-21 to -1	Day 1	Day 1	Day 1	Every 12 weeks or every 24 weeks as per above			30 days after End of Treatment[b]	Every 12 weeks
Window (Days)	–	–		± 7	± 7	± 7	–	–	± 7	± 14
Pulmonary function test[p]		X								
Concomitant medications review[q]	X	X	X	X	X	X	X	X	X	
Adverse event review[r]	X	X	X	X	X	X	X	X	X	
Efficacy Assessments[s]										
PET-CT[t]		X			X		X	X		
Contrast CT (chest, abdomen, pelvis and neck if clinically indicated)[t]		X			X	X	X	X		X
Bone marrow examination[u]		X					X			
Laboratory Assessments										
Hematology[v]		X	X	X	X	X			X	
Serum chemistry[w]		X	X	X	X	X			X	
Coagulation (prothrombin time, INR, aPTT)[x]		X	X	X	X	X			X	
Hepatitis serologies[y]		X				X				
Urinalysis[z]		X								
Pregnancy tests[aa]		X	X	X	X	X			X	
Zanubrutinib PK sample[bb]			X	X						
Other										

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Study Phase or Visit	Prescreening	Screening	Treatment (1 Cycle = 28 days)						Safety Follow-Up Visit after End of Treatment[b]	Long-Term Follow-up[c]
			Zanubrutinib Monotherapy				Suspected			
Cycle/Period[a]			Cycle 1	Cycle 2	Cycle 3	Every 12 weeks after C4D1 through the end of Year 2, then every 24 weeks	CR	PD		
Day		**-21 to -1**	**Day 1**	**Day 1**	**Day 1**	**Every 12 weeks or every 24 weeks as per above**			**30 days after End of Treatment[b]**	**Every 12 weeks**
Window (Days)	–	–		**± 7**	**± 7**	**± 7**	–	–	**± 7**	**± 14**
Survival status										**X**
Second primary malignances										**X**
Subsequent anticancer therapy									**X**	**X**

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BCL, B-cell lymphoma; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FDG, fluorodeoxyglucose; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; MYC, myelocytomatosis; PCR, polymerase chain reaction; PD, progressive disease; PET, positron emission tomography; QTcF, Fridericia's correction; RNA, ribonucleic acid.

Note: On Cycle 1 Day 1, all assessments unless otherwise noted should be performed predose.

[a] Treatment cycle length = 28 days.

[b] A Safety Follow-up Visit is conducted approximately 30 days (± 7 days) after the last dose of zanubrutinib, to perform the planned safety assessments and laboratory assessments, and to collect information on alternative anticancer therapy given after the last dose of study drug. Refer to Note q and Note r for more details about the collection of concomitant medications and adverse events, respectively.

[c] Long-term follow-up includes monitoring survival status, second primary malignances, subsequent therapies for DLBCL, and may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic progression. Visits repeat every 12 weeks (± 14 days) until the end of the study. For patients who permanently discontinue study drug treatment before radiographic progression is documented and confirmed by the investigator, tumor assessments will continue until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever comes first.

[d] Zanubrutinib will be administered orally as two 80-mg capsules twice a day (160 mg twice a day) with or without food. Patients will receive zanubrutinib monotherapy until disease progression, unacceptable toxicity, loss to follow-up, or the end of the study, whichever occurs first. A patient diary will be provided to each patient to record the zanubrutinib dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the site personnel for review and will be reviewed by the study coordinator on a regular basis.

[e] This must occur before any study-specific procedures are conducted for prescreening and screening and may be obtained before the 21-day screening window for the screening evaluations. Consent must be obtained using the current version of the form approved by the Independent Ethics Committee/Institutional Review Board.

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[f] Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted. Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6. The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

[g] Review any medical and cancer history any time after obtaining informed consent, including presence or absence of disease-related constitutional symptoms. Other background information including history of disease, including the date of initial diagnosis and current disease status, staging, and sites of disease. Prior medications/significant non-drug therapies and demographic data (gender, year of birth [or age] and race/ethnicity) will also be collected.

[h] Approximately 10 unstained slides must be sent to the central laboratory for detection of CD79B mutation status at the Prescreening Visit. A fresh tumor biopsy is preferred at prescreening. If fresh tumor biopsies are not available, then an archival tumor tissue taken within 2 years before prescreening will be requested.

[i] For patients who proceed to screening stage, 5 more unstained slides should be sent to the central laboratory for analysis of other potential predictors of response including assessment of subtypes, MYD88L265P mutation, and BCL2/MYC/TCL1A expression. DLBCL characteristic markers may also be assessed. Optional biopsy will be taken from patients who have confirmed disease progression during the study at accessible tumor sites to explore genetic alterations associated with drug resistance, including DNA alterations and analyses of the subtype (based on the gene expression profile).

[j] Blood samples will be collected at screening, time of first response, and time of disease progression. CD79B mutation status in the blood will be assessed. Blood-based biomarker analysis such as DNA/ctDNA alterations, etc, will be performed to explore their association with response, resistance, and prognosis.

[k] Safety assessments will be conducted on Day 1 of every cycle, unless otherwise specified.

[l] Vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) will be assessed after the patient has rested in the sitting position for 10 minutes. Vital signs will be performed at the Screening Visit, each visit during study treatment, and the Safety Follow-up Visit.

[m] Physical examination and weight will be performed at the Screening Visit, each visit during study treatment, and the Safety Follow-up Visit. Assessment of physical examination on the first day of Cycle 1 may be skipped if performed within previous 7 days. A complete physical examination is performed at the study site and includes an assessment of systems per standard of care and as clinically indicated by symptoms. 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. Height is determined at screening only.

[n] An echocardiogram/MUGA is to be performed at screening unless one has been performed within 30 days before the first dose of study drug.

[o] A 12-lead ECG will be performed in triplicate (≥ 1 minute apart) at screening and as clinically indicated. The calculated QTcF average of 3 ECGs must be ≤ 480 msec for eligibility. Patients should in a supine position and resting for at least 10 minutes before obtaining the ECGs.

[p] Pulmonary function test will be assessed at screening and as clinically indicated.

[q] Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 21days before the first dose of study drug, and on study thereafter until 30 days after the last dose of zanubrutinib. If any AE or SAE is reported during the prescreening phase, related medications should also be recorded in the eCRF.

[r] Any AE or SAE evaluated by the investigators as related to the procedures for study-relevant tumor tissue collection (eg, biopsy) after signing the prescreening informed consent form should be recorded in the eCRF. After the screening informed consent has been signed but before the administration of the study drug, only serious adverse events should be reported. After initiation of study drug, all adverse events and serious adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of zanubrutinib or the initiation of any alternative anticancer therapy, whichever comes first.

[s] Response will be assessed by the investigator according to the Lugano classification. Response parameters will include assessment of lymphadenopathy, hepatomegaly and splenomegaly, and bone marrow biopsy and aspirate.

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[t] All patients must have a baseline PET-CT and CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated (within 21days before the first dose of study drug). PET-CT should be done at screening, at Week 12 and Week 24 after treatment, and the time when CR or PD is suspected. For FDG non-avid disease, only CT scans will be required for post-baseline visit. Contrast CT should be performed at screening, every 12 weeks for 24 months, and every 24 weeks thereafter until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first. 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. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of PET-CT shall prevail. MRI and a non-contrast chest CT scan may be used instead of contrast CT for patients with serious contrast allergy; whichever method is used should be used consistently. Clinical suspicion of disease progression at any time will require radiologic confirmation to be performed promptly, rather than waiting for the next scheduled radiologic assessment.

[u] Bone marrow biopsy and aspirate must be performed at screening for all patients to assess bone marrow involvement of lymphoma if not performed within 60 days before the first dose as part of the standard care and there has been no intervening therapy from the time of the biopsy/aspirate until the start of study drug. For patients with bone marrow involvement of lymphoma at baseline, repeated bone marrow biopsy and aspirate are required if CR is suspected.

[v] Complete blood counts (CBC) with differential is required to be performed at screening (a repeated CBC test is required if not done within 7 days before the first dose of study drug), and at every visit during the treatment phase and the Safety Follow-up Visit. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell (WBC) count with differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

[w] Serum chemistry assessments include sodium, potassium, chloride, uric acid, bicarbonate/total carbon dioxide, glucose, urea or blood urea nitrogen, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, LDH, and alkaline phosphatase. Chemistry assessments are required at screening, every visit during the treatment phase, and the Safety Follow-up Visit.

[x] Coagulation assessments (prothrombin time, INR, aPTT) are required at screening, Day 1 of subsequent cycles, and the Safety Follow-up Visit.

[y] Hepatitis B serology includes HBsAg, HBcAb, and HBsAb. Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly (± 7 days) or at least every 90 days (± 7 days) for patients receiving prophylactic antiviral therapy. Hepatitis C serology includes HCV antibody. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly (± 7 days). Hepatitis B and hepatitis C testing may be performed by local laboratories if the laboratory is able to perform the tests to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C respectively); otherwise the results must be confirmed by the central laboratory.

[z] Urinalysis (which includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose) will be performed at screening.

[aa] A serum pregnancy test will be performed at screening and end of treatment for women of childbearing potential. Patients must have a negative serum pregnancy test at screening. Pregnancy tests must be performed at each visit during the treatment period and at the Safety Follow-up Visit. Any patient who is pregnant will not be eligible for the study. Subsequent tests in each visit may be urine tests, and if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after initiation of study treatment will be immediately withdrawn from participation in the study.

[bb] Pharmacokinetic samples for zanubrutinib will be collected sparsely at predose and 2 hours (± 30 minutes) postdose on Day 1 of Cycle 1 and Cycle 2. Procedures for collection of samples are described in the Laboratory Manual. Additional pharmacokinetic samples may be taken if needed. The investigator will record the actual time of blood collection on eCRF. Patients will also be instructed to record the dosing time of the evening dose at home (and be recorded on the eCRF) prior to coming in for the predose sample on Day 1 of Cycle 2.

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APPENDIX 2. LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

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[a] with or without a residual mass on 5PS[b,c] 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[b,c]	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

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Response and Site	PET-CT-Based Response	CT-Based Response
Lymph nodes and extra-lymphatic sites	Score 4 or 5[b,c] 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[b,c] 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
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:

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Response and Site	PET-CT-Based Response	CT-Based Response

		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[b,c] 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

Abbreviation: CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; 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] 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

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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), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and 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, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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

[c] 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 3. NEW YORK HEART ASSOCIATION CLASSIFICATION

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

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APPENDIX 4. CYP3A INHIBITORS AND INDUCERS

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

Abbreviation: CYP3A, cytochrome P450, family 3, subfamily A; HCV, hepatitis C virus.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (03 December 2019) (FDA 2019).

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

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

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APPENDIX 5. ECOG PERFORMANCE STATUS

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

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

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