CLINICAL PROTOCOL

Protocol Title:	A Phase 1, Open Label, Multiple Dose, Dose Escalation and Expansion Study of Bruton Tyrosine Kinase (BTK) Inhibitor, Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma
Protocol Number:	BGB-3111-110
Phase:	1
Investigational Product(s):	Zanubrutinib (BGB-3111)
Proposed Indication(s):	Diffuse large B-cell lymphoma
Sponsor:	BeiGene (Beijing) Co., Ltd. No. 30 Science Park Road Zhong-Guan-Cun Life Science Park Changping district Beijing, China 102206
Sponsor Medical Monitor:	[redacted]
Original Protocol Version 0.0:	20 May 2019
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FINAL PROTOCOL APPROVAL SHEET

A Phase 1, Open Label, Multiple Dose, Dose Escalation and Expansion Study of Bruton Tyrosine Kinase (BTK) Inhibitor, Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma

BeiGene (Beijing) Co., Ltd. Approval:

[redacted]

Sponsor Medical Monitor

INVESTIGATOR SIGNATURE PAGE

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene (Beijing) Co., Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene (Beijing) Co., Ltd.
Investigational Product(s):	Zanubrutinib (BGB-3111)
Title of Study:	A Phase 1, Open Label, Multiple Dose, Dose Escalation and Expansion Study of Bruton Tyrosine Kinase (BTK) Inhibitor, Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma
Protocol Identifier:	BGB-3111-110
Phase of Development:	1
Number of Patients:	The number of dose levels examined and the emerging toxicities of the combination therapy will determine the sample size. It is anticipated that approximately 27 patients in Part 1 and approximately 36 patients in Part 2 will be required. With an anticipated dropout rate of 10% for Part 2, approximately 67 patients will be enrolled.

Study Objectives:

Part 1

Primary:

- To determine the maximum tolerated doses (MTD) and the recommended Phase 2 dose (RP2D) of zanubrutinib in combination with lenalidomide, by dose escalation of lenalidomide in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL).
- To determine the safety and tolerability of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL by dose escalating lenalidomide.

Secondary:

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL as measured by overall response rate (ORR) assessed by investigator.
- To characterize the pharmacokinetic (PK) profiles of zanubrutinib and lenalidomide after a single dose and at steady state when given in combination.
- To evaluate the efficacy, as measured by ORR, based on the DLBCL subtypes.

Exploratory:

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide as measured by complete response rate (CRR), time to response (TTR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS), in patients with R/R DLBCL as well as in patients with different subtypes of R/R DLBCL.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes.
- To explore mechanisms of disease resistance.

Part 2

Primary:

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL as measured by ORR.

Secondary:

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide, as measured by CRR, TTR, PFS and DOR.
- To determine the safety and tolerability of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL.
- To further characterize the PK profiles of zanubrutinib and lenalidomide after single dose and at steady state when given in combination.
- To evaluate the efficacy (ORR, CRR, TTR, PFS, and DOR) based on the DLBCL subtypes.

Exploratory:

- To further evaluate the efficacy as measured by OS.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes (eg, ORR, CRR, PFS, TTR and DOR).
- To explore mechanisms of disease resistance.

Study Design:

This Phase 1 study is designed to assess the safety and efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL.

One cycle of treatment is 28 days in length.

Part 1

Part 1 will be the dose escalation portion, consisting of lenalidomide dose escalation with zanubrutinib fixed dose as the table below:

Dose Level	Zanubrutinib	Lenalidomide
Dose Level -1	160 mg BID	10 mg QD
Dose Level 1 (Starting dose)	160 mg BID	15 mg QD
Dose Level 2	160 mg BID	20 mg QD
Dose Level 3	160 mg BID	25 mg QD

BID=twice daily; QD=once daily

For dose escalation, 3+3 principles will be followed for MTD determination.

The dose of zanubrutinib will remain fixed with up to 3 dose levels of lenalidomide to be explored according to the table above. Zanubrutinib will be administered orally at 160 mg twice daily. Lenalidomide will be administered orally once daily at the designated dose levels in the table above on Days 1-21 of each 28-day cycle. Both zanubrutinib and lenalidomide will continue until disease progression or unacceptable toxicity.

PK blood sampling will be performed at predose (0 hr), 0.5, 1, 2, 3, 4, 8hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentrations.

After the RP2D of lenalidomide is defined, further enrollment into Part 2 will commence.

Part 2

Part 2 will be conducted as an open label, single arm, multicenter, expansion study with Simon's two-stage design. Eligible R/R DLBCL patients will receive zanubrutinib combined with lenalidomide. The dose of lenalidomide will be the RP2D identified in Part 1. Both treatment medications will continue until disease progression or unacceptable toxicity.

PK blood sampling will be performed for 12 patients from the first stage enrollment at predose (0 hr), 0.5, 1, 2, 3, 4, 8 hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentrations.

During Part 1 and 2, both immunohistochemistry (IHC) and gene expression profiling (GEP) will be used to assess enrolled patients' status with respect to subtype of DLBCL. IHC allows a distinction between patients as either non-germinal-center B-cell like (GCB) or GCB phenotype. With GEP, the patients can be further categorized into three subtypes: activated B-cell like (ABC), GCB and unclassified.

Study Assessments:

Response will be evaluated using the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (The Lugano Classification, 2014). All patients should undergo positron emission tomography (PET) and contrast computed tomography (CT) at screening; PET and contrast CT should be repeated every 12 weeks for the first 48 weeks, every 16 weeks for the next 48 weeks, and every 24 weeks thereafter until disease progression, use of alternative anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Response will be assessed on the basis clinical and radiologic evaluations. Bone marrow biopsy and aspiration will be required for confirmation of CT-based CR at first occurrence of radiologic and clinical evidence of CR in patients with bone marrow tumor involvement at baseline. 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.

The sponsor, leading investigator, and possibly other investigators will establish a Safety Monitoring Committee (SMC) for ongoing safety assessment throughout the study. The SMC charter will define the organization members and procedures. The SMC will evaluate safety data from the dose escalation portion (Part 1) and decide the dose level for next group or enroll more eligible patients, based on the safety data from the previous dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed.

Patients will be evaluated for adverse events (AEs) (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version [v]5.0) and serious adverse events (SAEs). Patients who have an AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

Key Eligibility Criteria:

Inclusion Criteria

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

1. Histologically confirmed DLBCL, all patients must provide sufficient archival or fresh tumor tissue samples for evaluation by immunohistochemistry (IHC) and GEP.
2. Relapsed or refractory disease, defined as either: 1) progression of disease after having achieved disease remission (complete response [CR] or partial response [PR]) at the latest treatment regimen or 2) stable disease (SD), or progressive disease (PD) at the completion of the latest treatment regimen preceding entry to the study.
3. Patients who have not received high dose therapy/stem cell transplantation (HDT/SCT) must be ineligible for HDT/SCT.
4. Men and women ≥18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
6. Measurable disease as defined by at least 1 nodal lesion >1.5 cm in longest diameter, or at least 1 extra-nodal lesion >1.0 cm in longest diameter, and measurable in 2 perpendicular dimensions.

7. Previously received at least 1 line of adequate systemic anti-DLBCL therapy, defined as an anti-CD20 antibody and an appropriate anthracycline-based combination therapy for at least 2 cycles, unless the patient is intolerant or had disease progression before Cycle 2.
8. Adequate hematologic function, defined as:
    a. Absolute neutrophil count (ANC) ≥1 x 10^9/L, independent of growth factor support for at least 7 days
    b. Platelet count ≥75 x 10^9/L, independent of growth factor support or transfusion for at least 7 days
    c. Hemoglobin >80 g/L, independent of transfusion for at least 7 days.
9. Adequate hepatic function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN)
    b. Bilirubin ≤2 x ULN (unless documented Gilbert's syndrome, then up to 5 x ULN allowed)
10. Adequate renal function, defined as creatinine clearance of ≥60 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]).
11. International normalized ratio (INR) ≤1.5 x ULN and activated partial thromboplastin time (aPTT) ≤1.5 x ULN.
12. Patients who relapse at least 100 days after autologous stem cell transplant may be enrolled.
13. Two negative pregnancy tests (at least one blood test) must be obtained for female patients of childbearing potential before initiating therapy. The first test must be performed within 10-14 days before lenalidomide therapy and the second test within 24 hours before lenalidomide therapy.
14. Female patients of childbearing potential must commit either to sexual abstinence or to use 2 methods of reliable birth control simultaneously (Section 5.2) beginning 4 weeks before initiating treatment with lenalidomide, throughout the course of the study and at least up to 90 days after last dose of zanubrutinib or lenalidomide, whichever is longer. Male patients will be eligible if abstinent, or must use a latex or synthetic condom (even if they have undergone a successful vasectomy) in combination with other highly effective contraception methods described in Section 5.2, and must not donate sperm, throughout the course of the study and at least up to 90 days after last dose of zanubrutinib or lenalidomide, whichever is longer.
15. Patients must not donate blood during treatment with lenalidomide and for 4 weeks after discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to lenalidomide.
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. Current or history of central nervous system (CNS) lymphoma.
2. Histologically transformed lymphoma.
3. History of allogeneic stem-cell transplantation.
4. Prior exposure to a BTK inhibitor.
5. Prior exposure to lenalidomide or thalidomide.

6. Receipt of the following treatment before first dose of study drug:
    a. Corticosteroids (at doses >20 mg/day prednisone equivalent) given with anti-neoplastic intent within 7 days.
    b. Chemotherapy or radiotherapy within 4 weeks.
    c. Monoclonal antibody within 4 weeks.
    d. Investigational therapy within 4 weeks.
    e. Chinese patent medicine with anti-neoplastic intent within 4 weeks.
    f. Chimeric antigen receptor T-cell (CAR-T) therapy.
7. Major surgery within 4 weeks before the first dose of study drug.
8. Toxicity of ≥ Grade 2 from prior anti-cancer therapy (except for alopecia, ANC, hemoglobin and platelets. For ANC, hemoglobin and platelets, please follow inclusion criterion #8.
9. History of other active malignancies within 2 years before study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
10. 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 msecs
    e. History of second-degree atrioventricular (AV) block Type II or third-degree AV block
    f. New York Heart Association (NYHA) class III or IV congestive heart failure
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at Screening
11. 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.
12. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
13. Unable to swallow capsules or having a disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
14. Uncontrolled systemic infection requiring parenteral intravenous anti-infective therapy.
15. Known human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (<20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
16. Known hypersensitivity to lenalidomide, or compounds of similar chemical or biologic composition to lenalidomide.

17. Pregnant or lactating women.
18. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, or put the study at risk.
19. Requires ongoing treatment with strong and moderate CYP3A inhibitors or inducers. If patients have been on a 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.
20. History of deep-vein thrombosis (DVT) or pulmonary embolism (PE) within the past 12 months.

Test Product, Dose, and Mode of Administration:

Zanubrutinib will be administered as two 80-mg capsules orally twice a day (160 mg twice daily) 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.

Lenalidomide will be administered orally daily with or without food on Day 1-21 of each 28-day cycle. Lenalidomide should be administered with water.

Reference Therapy, Dose, and Mode of Administration:

None.

Endpoints

Part 1

Primary Endpoints

- The safety of zanubrutinib combined with lenalidomide will be assessed throughout the study by monitoring AEs and SAEs, per the NCI-CTCAE v5.0, physical examination and laboratory measurements.
- The RP2D of lenalidomide will be determined based on safety data.

Secondary Endpoints

- ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification.
- PK evaluations for zanubrutinib and lenalidomide, as appropriate and allowed by the data:
  - Single dose: including but not limited to area under the plasma concentration-time curve from time zero to the last measurable time ($AUC_{(0-t)}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and apparent clearance after oral administration (CL/F).
  - Steady state: including but not limited to $AUC_{(0-t)}$, maximum plasma concentration at steady state ($C_{max,ss}$), T_{max}, minimal drug concentration at steady state (C_{trough}), CL/F, and accumulation ratio (Ro).
- Clinical outcomes as measured by ORR based on the GCB and non-GCB identified by IHC and ABC and GCB subtype identified by GEP.

Exploratory Endpoints

- Efficacy endpoints of zanubrutinib combined with lenalidomide, including CRR, DOR, PFS, TTR and OS, in the efficacy analysis set as well as subgroups classified by IHC and by GEP. Exploratory efficacy endpoints as determined by investigator are as follows:
  - CRR, defined as the proportion of patients whose BORs are CR based on the Lugano classification in the efficacy analysis set of dose escalation.
  - DOR, defined as the time from the first response documentation to the date that progression is documented after treatment initiation or death, whichever occurs first.
  - PFS, defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first
  - TTR, defined as the time from treatment initiation to the first documentation of response.
  - OS, defined as the time from treatment initiation until death.
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR, OS) by clinical/genetic risk factors.
- Potential resistance biomarkers and mechanisms of resistance.

Part 2

Primary Endpoint

- The primary endpoint of Part 2 of is the ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification.

Secondary Endpoints

- Clinical outcomes of zanubrutinib combined with lenalidomide, as determined by investigators, including CRR, DOR, PFS and TTR, in the efficacy analysis set.
- The safety and tolerability of zanubrutinib combined with lenalidomide will be assessed throughout the study by monitoring AEs and SAEs, per the NCI-CTCAE v5.0, physical examination and laboratory measurements.
- PK evaluations for zanubrutinib and lenalidomide. as appropriate and allowed by the data:
  - Single dose: including but not limited to $AUC_{(0-t)}$, C_{max}, T_{max}, CL/F.
  - Steady state: including but not limited to $AUC_{(0-t)}$, $C_{max,ss}$, T_{max}, C_{trough}, CL/F, Ro.
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR) based on the GCB and non-GCB identified by IHC and ABC and GCB subtype identified by GEP.

Exploratory Endpoints

- Overall survival (OS)
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR, OS) by clinical/genetic risk factors.
- Potential resistance biomarkers and mechanisms of resistance.

Sample size determination:

Sample size for Part 1 will depend on the number of dose levels examined and the emerging toxicities of the combination therapy. It is expected the number of patients in Part 1 will be approximately 27 patients.

For Part 2, Simon's two-stage design will be used. The null hypothesis that the true response rate is 0.25 will be tested against a one-sided alternative. In the first stage, if there are 4 or fewer responses in these 18 patients, the study will be stopped. The null hypothesis will be rejected if 15 or more responses are observed in 36 patients. This design yields a type I error rate of 0.025 and power of 96% when the true response rate is 0.55.

With an anticipated dropout rate of 10% for Part 2, approximately 67 patients will be enrolled.

Statistical Methods:

Efficacy data in Parts 1 and 2 will be summarized separately.

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

Safety analysis set is defined as all patients who are exposed to at least one dose of any medication within the combination therapy. Efficacy analysis set is defined as all patients who are exposed to at least one dose of any medication with confirmed R/R DLBCL. Patients with no post-baseline response assessments will be treated as non-responders. It will be used as the primary analysis set for all the efficacy analyses. Efficacy evaluable analysis set is defined as all patients who are exposed to at least one dose of any medication with confirmed R/R DLBCL and have at least one post-baseline response assessment unless discontinued treatment due to clinical progression or death prior to response assessment in the efficacy analysis set. It will be used for sensitivity analyses. All patients who have at least one post dose plasma concentration and no major protocol deviation affecting PK would be included in the PK analysis set.

ORR and CRR will be determined in the efficacy analysis set along with 95% confidence interval (CI) using Clopper-Pearson method.

Kaplan-Meier methodology will be used to estimate TTR, DOR, PFS and OS medians, and their 95% CI will be constructed using Brookmeyer and Crowley method. Kaplan-Meier curves will also be provided.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABC	activated B-cell like
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the curve
BTK	Bruton tyrosine kinase
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CR	complete response
CRR	complete response rate
CT	computed tomography
C_{trough}	minimal drug concentration (trough) at steady state
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
GCB	germinal-center B-cell like
GEP	gene expression profiling
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high dose therapy
IEC	independent ethics committee
IHC	immunohistochemistry
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging

Abbreviation	Definition
MTD	maximum tolerated dose
NCI-CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
NHL	non-Hodgkin lymphoma
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
R/R	relapsed or refractory
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCT	stem cell transplant
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal

1. INTRODUCTION

1.1. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive non-Hodgkin lymphomas (NHL) in the United States, with an annual incidence that has been rising gradually since the 1990s (Fisher and Fisher 2004). It is estimated that 72,580 new NHL patients will be diagnosed in the US in 2016, with 20,150 dying from the disease (Siegel 2013). DLBCL accounts for approximately 32.5% of NHLs diagnosed annually (Al-Hamadani 2015). The estimated rate for DLBCL is approximately 4.68 cases per 100,000 person-years. Based on the study report of National Central Cancer Registry of China, an estimated 88,200 new lymphoma cases and 52,100 lymphoma deaths would occur in China in 2015, ranked in the 12th and 11th place among all cancer cases, respectively (Chen 2016); According to one retrospective analysis for lymphoma subtype distribution conducted by China Lymphoma Study Group, DLBCL makes up about 40.8% of NHL cases and 35.8% of all lymphoma cases (Li 2012). According to the 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.

The major clinical prognostic factors for NHL are well described and have been incorporated into the International Prognostic Index (IPI) scoring system. The specific factors are: age >60 years, stage III or IV disease, performance status ≥2, elevated lactate dehydrogenase (LDH) levels, and extranodal involvement >1 site. These factors are combined in the IPI into 4 categories, with 5-year progression-ree survival (PFS) ranging from 40% to 70% and 5-year overall survival (OS) ranging from 26% to 73% among patients treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (Ziepert 2010)..

1.1.1. Subtype of DLBCL

Diffuse large B-cell lymphoma is a heterogeneous disease not only clinically, but also morphologically and molecularly. Recent progress has been made in terms of understanding and categorizing the molecular heterogeneity of DLBCL. In a retrospective analysis of a large series of patients with DLBCL, the Leukemia and Lymphoma Molecular Profiling Project used deoxyribonucleic acid (DNA) microarray to identify distinct gene-expression profiles on the basis of hierarchical clustering (Rosenwald 2002). Two principal independent gene-expression subgroups were identified: germinal-center B-cell-like (GCB) and activated B-cell-like (ABC). After standard chemotherapy, the GCB and ABC subgroups were not only prognostically distinct in direct comparison (with superior outcome in the GCB subgroup), but this prognostic distinction was also independent of the IPI. Therefore, it has provided novel insights into the pathogenesis of the respective DLBCL, identified molecules which provided targets for novel "targeted therapies" drugs. Incorporating these new drugs into combination immuno-chemotherapy might result in even higher cure rates of and/or less toxicity for patients with DLBCL.

1.2. Standard Treatment of DLBCL

The current standard regimen for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), which achieves a cure in many patients. In clinical practice, the treatment decision is also determined based on various factors such as the stage, age, presence of bulky disease, and IPI. Despite recent progress in improving prognosis, 30-40% patients develop relapsed/refractory disease and have poor outcomes. High dose therapy (HDT) and stem cell transplant (SCT) offer a second chance for a cure, however, for those patients not eligible for HDT/SCT, both the U.S. National Comprehensive Cancer Network (NCCN) (NCCN 2018) and the European Society for Medical Oncology (ESMO) recommend inclusion in a clinical study whenever possible (Tilly 2015).

1.3. Bruton Tyrosine Kinase and B-cell Lymphoma

B-cell receptor (BCR) signaling is essential for normal B-cell differentiation and function. In addition, several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies. First, expression of a functional BCR is maintained throughout lymphoma progression even as the non-expressed immunoglobulin heavy chain is involved in oncogenic translocations and despite prolonged treatment of tumor cells with anti-idiotype therapies (Küppers 2005; Meeker 1985). Also, selective knockdown of BCR components by ribonucleic acid (RNA) interference results in apoptosis in multiple B-cell lymphoma cell lines (Gururajan 2006).

Recent studies indicate that chronic active BCR signaling is a pathogenic mechanism in ABC

DLBCL and this chronic activation engages the classic nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway; in contrast GCB DLBCL pathogenesis is independent of this pathway (Lenz and Staudt 2010). This difference in the molecular mechanism of pathogenesis (ie, constitutive activation of NF-κB in ABC DLBCL) may explain why the ABC subtype is less sensitive to chemotherapy and remains less curable than the GCB subtype.

Bruton tyrosine kinase (BTK) plays an essential role in the chronic active BCR signaling cascade in which engages NF-κB activation in wild-type Caspase Recruitment Domain Family Member 11 (CARD11) ABC DLBCL. In vitro data targeting this pathway in ABC DLBCL cells was recently reported by Davis and colleagues (Davis 2010). Activated B-cell like DLBCL cell lines with constitutive BCR signaling undergo cell death when treated with ibrutinib, while these drugs had no effect on ABC and GCB DLBCL cell lines that did not rely on constitutive BCR signaling. Clinical evidence that targeting the NF-κB pathway has a favorable response to outcome in ABC versus GCB subtypes was reported by Dunleavy and colleagues (Dunleavy 2009). They showed in a Phase 2 study that bortezomib, which indirectly targets the NF-κB pathway by inhibiting proteasome degradation of BAY117085 for NF-κB pathway (IκBĮ), in combination with chemotherapy had a response rate of 85% in ABC subtype versus 13% in GCB subtype (P=0.0004). Thus, inhibition of the BCR-NF-κB pathway by blocking BTK activity may represent a novel therapeutic strategy in ABC DLBCL.

1.4. Zanubrutinib

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

1. Zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, including EGFR, FGR, FRK, HER2, HER4, ITK, JAK 3, LCK, and TEC, which may reduce toxicities possibly due to off-target inhibition such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue.
2. Zanubrutinib has improved oral bioavailability.

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 Investigator's Brochure).

Zanubrutinib is a potent, specific and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nM. Cellular assays confirm that zanubrutinib inhibits BCR aggregation-triggered BTK autophosphorylation and blocks downstream phospholipase C gamma 2 signaling in mantle cell lymphoma (MCL) cell lines. Zanubrutinib had an IC_{50} of 1.8 nM in a homogeneous time-resolved fluorescence-based BTKpY223 assay. It potently and selectively inhibited cellular growth of several MCL cell lines (REC-1, Mino and JeKo-1), and the activated B-cell type DLBCL cell line 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 is significantly more effective than ibrutinib when inducing dose-dependent antitumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib also demonstrated better antitumor activity than ibrutinib in TMD-8 DLBCL subcutaneous xenograft model. In a PK/pharmacodynamics study, oral administration of zanubrutinib resulted in time-dependent occupancy of BTK in blood and in spleen in mice and was approximately 3-fold more potent than ibrutinib in mouse pharmacodynamic assays.

In a panel of 342 human kinases, 1 μM zanubrutinib inhibited only 12 other kinases by > 70%. Zanubrutinib was more selective than ibrutinib for inhibition of kinase activity of BTK EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold).

Cytochrome P450 (CYP) phenotyping in human liver microsomes suggests that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism. Zanubrutinib is a weak reversible inhibitor toward CYP2C8 and intestinal (not hepatic) CYP3A4, and does not display clinically relevant time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Zanubrutinib is a weak inducer of CYP2B6 and CYP3A4, but does not induce CYP1A2. Although zanubrutinib is a sensitive CYP3A4 substrate, it does not have a clinically relevant effect on its own exposure. Zanubrutinib may inhibit BCRP and P-gp transport at clinical doses. The coadministration of oral P-gp or BCRP substrates with a narrow therapeutic index (eg, digoxin, methotrexate) with zanubrutinib may increase their concentrations. Zanubrutinib does not inhibit the hepatic uptake transporters, OATP1B1 and OATP1B3, or the renal uptake transporters, 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 either rats or 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 was 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

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) indicated that co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once daily for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$, 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 daily for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

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 study showed that zanubrutinib has no effect on CYP2C9 enzyme and BCRP activity. Zanubrutinib is shown to be a mild CYP3A4 and CYP2C19 inducer per FDA guidelines. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib. Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}.

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

1.4.3. Summary of Relevant Clinical Experience with Zanubrutinib

1.4.3.1. Dose Selection for Zanubrutinib

A first-in-human study (BGB-3111-AU-003) that investigated the safety and PK of zanubrutinib in patients with hematologic malignancy. The preliminary data showed that the maximum observed concentration (C_{max}) and area under the concentration curve (AUC) increased in a nearly dose-proportional manner from 40 mg to 320mg after singe-dose administration and at steady-state during repeat-dose administration (zanubrutinib Investigator's Brochure). The absorption of zanubrutinib is rapid, with a median time to maximum plasma concentration (C_{max}) of 2 hours. The mean $t_{1/2}$ was between 2 to 4 hours with minimal accumulation observed after repeated dosing. Results from a food effect study showed that zanubrutinib exposure was not altered by a high-fat breakfast. Mean area under the curve (AUC) and C_{max} were increased by 12% and 51% by a low-fat breakfast, respectively. The 51% and 12% increases in the geometric means of C_{max} and AUC_{0-inf} observed when zanubrutinib was given with a low-fat meal as compared to the fasted state are not considered to be clinically relevant, as these increases fall within the range of exposures in which zanubrutinib is safe and well-tolerated, therefore, zanubrutinib can be administered with or without food.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice daily and 320 mg once daily (Tam 2015). At the 160 mg twice daily dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including chronic lymphocytic leukemia, MCL, Waldenström macroglobulinemia and follicular lymphoma) at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive experience at the 160 mg twice daily and 320 mg once daily doses, 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 daily 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.

1.4.3.2. Preliminary Efficacy and Safety Data for Zanubrutinib

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

1.5. Lenalidomide

Lenalidomide is currently approved in the United States for the treatment of relapsed or refractory MCL at a recommended starting dose of 25 mg orally once daily for 21 days every 28 days.

Lenalidomide is a more potent molecular analog of thalidomide, in vitro, lenalidomide has three main activities: direct anti-tumor effect, inhibition of angiogenesis, and immunomodulation. In vivo, lenalidomide induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, by anti-angiogenic and anti-osteoclastogenic effects, and by immunomodulatory activity. Lenalidomide has a broad range of activities that can be exploited to treat many hematologic and solid cancers.

Lenalidomide is rapidly absorbed after oral administration. After single and multiple doses of lenalidomide in patients with multiple myeloma (MM) or myelodysplastic syndrome (MDS), the maximum plasma concentrations occurred at 1 hour (approximately 0.5-6 hours) postdose. Multiple doses of lenalidomide at the recommended dosage does not result in drug accumulation. Administration of a single 25 mg dose of lenalidomide with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in C_{max}. In the studies where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. The prescribing information of lenalidomide suggested lenalidomide can be administered with or without food. The mean half-life of lenalidomide is 3 to 5 hours in patients with MM, MDS or MCL. Lenalidomide is not anticipated to be subjected to pharmacokinetic drug-drug interactions when co-administered with CYP inhibitors, inducers, or substrates. Despite being a weak substrate of P-gp in vitro, lenalidomide does not have clinically significant pharmacokinetic interactions with P-gp substrates/inhibitors in controlled studies. Renal function is the only important factor affecting lenalidomide plasma exposure, starting dose need to be adjusted based on the creatinine clearance value (<60 mL/min). Age (39 to 85 years), body weight (33 to 135 kg), sex, race, and type of hematological malignancies (MM, MDS or MCL) did not have a clinically relevant effect on lenalidomide clearance in adult patients.

The safety data for 134 patients receiving monotherapy for MCL has been evaluated. The most common treatment-emergent adverse events (AEs) (>15%) were neutropenia (49%), thrombocytopenia (36%), fatigue (34%), diarrhea (31%), anemia (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritis (17%), constipation (16%), and peripheral edema (16%). The most common Grade 3 or 4 adverse events were hematologic in nature: neutropenia (43%), thrombocytopenia (28%), and anemia (11%). Pneumonia (9%) was the most frequent non-hematologic Grade 3 or 4 adverse event.

The median duration of treatment in this patient population was 95 days (1-1002 days). Seventy-six patients (57%) required at least one dose interruption for an AE, while 51 patients (38%) had at least one dose reduction due to toxicity. Twenty-six patients (19%) discontinued treatment due to AEs.

Lenalidomide has a black box warning for embryo-fetal toxicity, hematologic toxicity and venous and arterial thromboembolism.

1.5.1. Venous and Arterial Thromboembolism

Venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism (PE), has been reported in patients during treatment for NHL generally, occurring at incidences from approximately 7% up to 20% (Zhou 2010; Park 2012; Lyman 2013). In lenalidomide clinical studies, DVT and PE were reported in 7 (2.6%) and 6 (2.2%) of 266 subjects with relapsed or refractory NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik 2008; Witzig 2011). Anti-thrombotic prophylaxis was not suggested in NHL-002 but was required for subjects considered to be at high risk of developing DVT in NHL-003. Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (eg, hyperlipidemia, hypertension, smoking).

1.5.2. Second New Cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

1.5.3. Serious Infection due to Neutropenia

In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 4 and ≥ Grade 3 infections have occurred in the context of neutropenia (any grade). Lenalidomide treatment in combination with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of Grade 4 neutropenia compared to placebo-dexamethasone treated patients. Patients should report signs and symptoms of infection promptly.

1.5.4. Embryo-fetal Toxicity

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.

In the current study, two negative pregnancy tests must be obtained prior to initiating therapy. Contraception must begin 4 weeks before initiating treatment with lenalidomide, throughout the course of the study and at least up to 90 days after last dose of lenalidomide.

For more complete safety information, refer to the prescribing information (REVLIMID® Prescribing Information 2019).

2. STUDY OBJECTIVES

2.1. Part 1

2.1.1. Primary

- To determine the maximum tolerated doses (MTD) and the recommended Phase 2 dose (RP2D) of zanubrutinib in combination with lenalidomide by dose escalation of lenalidomide in patients with relapsed/refractory (R/R) DLBCL.
- To determine the safety and tolerability of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL by dose escalating lenalidomide.

2.1.2. Secondary

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide, in patients with R/R DLBCL as measured by overall response rate (ORR) assessed by investigator.
- To characterize the pharmacokinetic (PK) profiles of zanubrutinib and lenalidomide after single dose and at steady state when given in combination.
- To evaluate the efficacy, as measured by ORR, based on the DLBCL subtypes.

2.1.3. Exploratory

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide, as measured complete response rate (CRR), time to response (TTR), duration of response (DOR), PFS and OS, in patients with R/R DLBCL as well as in patients with different subtypes of R/R DLBCL.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes.
- To explore mechanisms of disease resistance.

2.2. Part 2

2.2.1. Primary

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL as measured by ORR.

2.2.2. Secondary

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide, as measured by CRR, TTR, DOR and PFS.
- To determine the safety and tolerability of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL.

- To further characterize the PK profiles of zanubrutinib and lenalidomide after single dose and at steady state when given in combination.
- To evaluate the efficacy (ORR, CRR, TTR, PFS, and DOR) based on the DLBCL subtypes.

2.2.3. Exploratory

- To further evaluate the efficacy as measured by OS.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes (eg, ORR, CRR, PFS, TTR, DOR, and OS).
- To explore mechanisms of disease resistance.

3. STUDY DESIGN

3.1. Study Rationale

3.1.1. Rationale for Combination

Ibrutinib has demonstrated single agent activity in the treatment of R/R DLBCL. In a phase 1/2 clinical study that involved 80 patients with R/R DLBCL, ibrutinib produced complete or partial responses in 37% (14/38) of those with ABC DLBCL, but in only 5% (1/20) of patients with GCB DLBCL (P = 0.0106) (Wilson 2015). A similar result is seen in an ongoing, single-arm, phase 2 study of zanubrutinib in patients with R/R non-GCB DLBCL.

Lenalidomide is a second-generation immunomodulatory imide drug (IMiD) that is also interesting to consider with respect to targeting BCR signaling in DLBCL. A phase 2/3 randomized study was conducted in patients with R/R DLBCL. Lenalidomide treated patients had an ORR of 27.5% versus 11.8% in investigator's choice (ORR were similar regardless of IHC-defined DLBCL subtype). Median PFS was increased in patients receiving lenalidomide (13.6 weeks) versus investigator's choice (7.9 weeks; P=0.041), with greater improvements in non-GCB patients (15.1 vs. 7.1 weeks, respectively; P=0.021) compared with GCB (10.1 vs. 9.0 weeks, respectively; P=0.550). Exploratory analyses suggested that this preferential benefit was more pronounced in the GEP-defined ABC population (Czuczman 2017).

Preclinical studies document the potential synergy of ibrutinib and lenalidomide in the treatment of ABC DLBCL based upon their mechanism of action and specificity for the genetic alterations seen in ABC DLBCL (Yang 2012). ABC DLBCL tumors depend upon both the BCR and MYD88 signal pathways for survival. Lenalidomide kills ABC DLBCL cells by augmenting interferon b (IFNb) production, owing to the oncogenic MYD88 mutations in these lymphomas. In a cereblon-dependent fashion, lenalidomide down regulates IRF4 and SPIB, transcription factors that together prevent IFNb production by repressing IRF7 and amplify prosurvival NF-kB signaling by transactivating CARD11. Blockade of B-cell receptor signaling using the BTK inhibitor ibrutinib also down regulates IRF4 and consequently synergizes with lenalidomide in killing ABC DLBCLs, suggesting attractive therapeutic strategies.

Preclinical study also demonstrated that combining zanubrutinib and lenalidomide may lead to synergetic effect.

In a phase 1 clinical study which involved 25 R/R B-NHL patients (9 DLBCL), combined therapy with ibrutinib and lenalidomide in B-NHL was well tolerated. Preliminary efficacy was observed in R/R DLBCL patients, ORR was 33%. (Christian 2015).

Based upon the safety profile of zanubrutinib monotherapy and the lack of significant myelosuppression, the combination of lenalidomide and zanubrutinib may be well tolerated with the potential to exploit synergistic effects for improvement in outcomes in a frail population with minimal therapeutic options and poor prognosis.

3.1.2. Rationale for Dose

The rationale for the current dose and schedule of each agent is based not only upon the approved dose for these treatments, but also based upon the safety data known regarding the use of these therapies for the treatment of NHL in the relapsed and refractory setting. Besides, based on metabolic profiles of zanubrutinib and lenalidomide, these two drugs are not expected to have PK-related drug-drug interaction when co-administered.

The established dose in monotherapy studies of lenalidomide is 25 mg administered orally once daily for 21 days of a 28-day cycle (Witzig 2011).

The escalation cohort will begin lenalidomide at one dose level with a dose level-1 built in to allow for further evaluation of the 2-drug combination if a lower lenalidomide dose is needed. Since zanubrutinib has been studied at the 320 mg dose on a continuous daily dosing schedule and is well tolerated, it will be administered daily until disease progression or unacceptable toxicity.

3.2. Summary of Study Design

This Phase 1 study is designed to assess the safety and efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL.

One cycle of treatment is 28 days in length.

3.2.1. Part 1

Part 1 will be the dose escalation portion, consisting of lenalidomide dose escalation with zanubrutinib fixed dose as the table below:

Table 1: Part 1 Dosing Levels

Dose Level	Zanubrutinib	Lenalidomide
Dose Level -1	160 mg BID	10 mg QD
Dose Level 1 (Starting dose)	160 mg BID	15 mg QD
Dose Level 2	160 mg BID	20 mg QD
Dose Level 3	160 mg BID	25 mg QD

BID=twice daily; QD=once daily

For dose escalation, 3+3 principles will be followed for MTD determination.

The dose of zanubrutinib will remain fixed with up to 3 dose levels of lenalidomide to be explored according to Table 1. Zanubrutinib will be administered orally at 160 mg twice daily. Lenalidomide will be administered orally once daily at the dose designated by dose levels in Table 1 on Days 1-21 of each 28-day cycle. Both zanubrutinib and lenalidomide will continue until disease progression or unacceptable toxicity.

The starting dose of lenalidomide will be 15 mg/day. The dose-limiting toxicity (DLT) observation period is 28 days (1 cycle) of therapy followed by evaluation for toxicity on Cycle 2 Day 1.

Enrollment will proceed as follows:

- If no DLT is observed during the DLT observation period in the initial 3 patients of a cohort (0/3), dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed, 3 additional patients will be enrolled at the same dose level for a total of at least 6 patients. If no further DLT(s) are observed (1/6), escalation to the next higher dose level cohort will occur.
- If 2 or more DLTs (≥2/6) are observed in the 6 patients, the MTD is considered to have been exceeded and no further patients will be enrolled at that dose.
- If there are 2 or more DLTs in Dose Level 1, Dose Level -1 will be enrolled.
- The MTD is defined as the highest dose at which <33% of the patients enrolled at one dose level experience a DLT. If all evaluated dose levels demonstrate an observed incidence of DLT in <33% of patients, the MTD of lenalidomide in the combination has not been reached. At least 6 patients should be treated at the MTD or highest tested dose.
- If a patient experiences a DLT during the DLT observation period, the patient will discontinue treatment.
- The decision to proceed to the next dose level or an interim dose level will be made in a Dose Level Review Meeting by the sponsor in conjunction with the investigators after careful consideration of all available safety and laboratory information. Safety data from patients on preceding cohorts that remain on continuous dosing will also be considered.
- According to study results and other relevant information, more additional patients, up to 12 patients, may be allowed to enroll to tested doses at or below MTD by SMC to collect more safety data.

3.2.1.1. Dose-Limiting Toxicity

A DLT is defined as events related to the study treatment as below:

- Hematologic:
  - Grade 4 neutropenia lasting for > 7 days, despite growth factor support
  - ≥ Grade 3 neutropenia with a fever ≥ 38.3ºC
  - Grade 4 thrombocytopenia lasting for > 7 days, despite holding treatment
  - Grade 3 thrombocytopenia with ≥ Grade 2 bleeding or requiring RBC or platelet transfusions

- Non-Hematologic:
  - Any Grade 3 or higher non-hematologic adverse event (Note: excludes asymptomatic chemistry abnormalities that are not clinically significant and resolve to Grade 2 or better in < 7 days)
  - ≥ Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting > 7 days
  - ≥ Grade 3 fatigue persisting for > 7 days
  - Treatment delay of any drug > 7 days for toxicity

In the Dose Escalation Phase, if a patient is non-compliant with the prescribed therapy or ends treatment within the first cycle for reasons other than study drug(s) related toxicity, ie, withdraws consent, they will be replaced. Any patient that misses >4 doses of zanubrutinib or lenalidomide for reasons other than toxicity will be replaced.

PK blood sampling will be performed at predose (0 hr), 0.5, 1, 2, 3, 4, 8hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentration.

After the RP2D of lenalidomide is defined, further enrollment into Part 2 will commence.

3.2.2. Part 2

Part 2 will be conducted as an open label, single arm, multicenter, expansion study with Simon's two-stage design. Eligible R/R DLBCL patients will receive zanubrutinib combined with lenalidomide. The dose of lenalidomide will be based upon the RP2D identified in Part 1. Both treatment medications will continue until disease progression or unacceptable toxicity.

PK blood sampling will be performed for 12 patients from the first stage enrollment at predose (0 hr), 0.5, 1, 2, 3, 4, 8 hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentration.

During Part 1 and 2, both IHC and GEP will be used to assess enrolled patients' status with respect to subtype of DLBCL. IHC allows a distinction between patients as either non-GCB or GCB phenotype. With GEP, the patients can be further categorized into three subtypes: ABC, GCB and unclassified.

3.3. Study Assessments

Response will be evaluated using the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (The Lugano Classification) (Cheson 2014). All patients should undergo positron emission tomography (PET) and contrast computed tomography (CT) at screening; PET and contrast CT should be repeated every 12 weeks for the first 48 weeks, every 16 weeks for the next 48 weeks, and every 24 weeks thereafter until disease progression, use of alternative anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Response will be assessed on the basis clinical and radiologic evaluations. Bone marrow biopsy and aspiration will be required for confirmation of CT-based CR at first occurrence of radiologic and clinical evidence of CR in patients with bone marrow tumor involvement before study drug. 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.

The sponsor, leading investigator and possibly other investigators will establish a Safety Monitoring Committee (SMC) for ongoing safety assessment throughout the study. The SMC charter will define the organization members and procedures. The SMC will evaluate safety data from the dose escalation potion (Part 1) and decide the dose level for next group or enroll more eligible patients, based on the safety data from the former dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed. In the case of major toxicity or efficacy concerns, the SMC can recommend modifying the study conduct.

Patients will be evaluated for adverse events (AEs) (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version [v]5.0) and serious adverse events (SAEs). Patients who have an AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

3.4. Blinding

Treatment with zanubrutinib, and lenalidomide is open-label.

4. ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

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

1. Histologically confirmed DLBCL, all patients must provide sufficient archival or fresh tumor tissue samples for evaluation by immunohistochemistry (IHC) and gene expression profiling (GEP).
2. Relapsed or refractory disease, defined as either: 1) progression of disease after having achieved disease remission (complete response [CR] or partial response [PR]) at the latest treatment regimen or 2) stable disease (SD), or progressive disease (PD) at the completion of the latest treatment regimen preceding entry to the study.
3. Patients who have not received HDT/SCT must be ineligible for HDT/SCT.
4. Men and women ≥18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
6. Measurable disease as defined by at least 1 nodal lesion >1.5 cm in longest diameter, or at least 1 extra-nodal lesion >1.0 cm in longest diameter, and measurable in 2 perpendicular dimensions.
7. Previously received at least 1 line of adequate systemic anti-DLBCL therapy, defined as an anti-CD20 antibody and an appropriate anthracycline-based combination therapy for at least 2 cycles, unless the patient is intolerant or had disease progression before Cycle 2.
8. Adequate hematologic function, defined as:
    a. Absolute neutrophil count (ANC) ≥1 x 10^9/L, independent of growth factor support for at least 7 days.
    b. Platelet count ≥75 x 10^9/L, independent of growth factor support or transfusion for at least 7 days.
    c. Hemoglobin >80 g/L, independent of transfusion for at least 7 days.
9. Adequate hepatic function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN).
    b. Bilirubin ≤2 x ULN (unless documented Gilbert's syndrome, then up to 5 x ULN allowed).
10. Adequate renal function, defined as creatinine clearance of ≥60 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]).
11. International normalized ratio (INR) ≤1.5 x ULN and activated partial thromboplastin time (aPTT) ≤1.5 x ULN.
12. Patients who relapse at least 100 days after autologous stem cell transplant may be enrolled.

13. Two negative pregnancy tests (at least one blood test) must be obtained for female patients of childbearing potential before initiating therapy. The first test must be performed within 10-14 days before lenalidomide therapy and the second test within 24 hours before lenalidomide therapy.
14. Female patients of childbearing potential must commit either to sexual abstinence or to use 2 methods of reliable birth control simultaneously (Section 5.2) beginning 4 weeks before initiating treatment with lenalidomide, throughout the course of the study and at least up to 90 days after last dose of zanubrutinib or lenalidomide, whichever is longer. Male patients will be eligible if abstinent, or must use a latex or synthetic condom (even if they have undergone a successful vasectomy) in combination with other highly effective contraception methods described in Section 5.2, and must not donate sperm, throughout the course of the study and at least up to 90 days after last dose of zanubrutinib or lenalidomide, whichever is longer.
15. Patients must not donate blood during treatment with lenalidomide and for 4 weeks after discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to lenalidomide.
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. Current or history of central nervous system (CNS) lymphoma.
2. Histologically transformed lymphoma.
3. History of allogeneic stem-cell transplantation.
4. Prior exposure to a BTK inhibitor.
5. Prior exposure to lenalidomide or thalidomide.
6. Receipt of the following treatment before first dose of study drug:
    a. Corticosteroids (at doses >20 mg/day prednisone equivalent) given with anti-neoplastic intent within 7 days.
    b. Chemotherapy or radiotherapy within 4 weeks.
    c. Monoclonal antibody within 4 weeks.
    d. Investigational therapy within 4 weeks.
    e. Chinese patent medicine with anti-neoplastic intent within 4 weeks.
    f. Chimeric antigen receptor T-cell (CAR-T) therapy.
7. Major surgery within 4 weeks before the first dose of study drug.
8. Toxicity of ≥ Grade 2 from prior anti-cancer therapy (except for alopecia, ANC, hemoglobin and platelets. For ANC, hemoglobin and platelets, please follow inclusion criteria #8.

9. History of other active malignancies within 2 years before study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
10. 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 msecs
    e. History of second-degree atrioventricular (AV) block Type II or third-degree AV block
    f. New York Heart Association (NYHA) class III or IV congestive heart failure (see Appendix 2)
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at Screening.
11. 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.
12. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
13. Unable to swallow capsules or having a disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
14. Uncontrolled systemic infection requiring parenteral intravenous anti-infective therapy.
15. Known human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (<20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
16. Known hypersensitivity to lenalidomide, or compounds of similar chemical or biologic composition to lenalidomide.
17. Pregnant or lactating women.
18. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, or put the study at risk.

19. Requires ongoing treatment with a strong and moderate CYP3A inhibitors or inducers (Appendix 4). If patients have been on a 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.
20. History of deep-vein thrombosis (DVT) or pulmonary embolism (PE) within the past 12 months.

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 6).

5.1. Informed Consent

At the screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the informed consent form will be given to the patient to read, and the patient must have adequate time to understand the content and ask questions.

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted, unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 28-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 is allowed if the patient did not previously meet the inclusion and exclusion criteria, or if needed to have a documented result within the protocol-specified screening window.

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

5.2. Females of Childbearing Potential and Contraception

A female is considered of childbearing potential, ie, fertile, after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 consecutive months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 consecutive months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

Female patients of childbearing potential must commit either to sexual abstinence or to use 2 methods of reliable birth control simultaneously beginning 4 weeks before initiating treatment with lenalidomide, throughout the course of the study and at least up to 90 days after last dose of zanubrutinib or lenalidomide, whichever is longer.

Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (e.g., 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.

Two methods of reliable birth control consist of one highly effective form of contraception and one additional effective contraceptive method.

Highly effective contraception methods include the following:

- Tubal ligation
- An intrauterine device
- Hormonal (e.g., oral, injectable, intravaginal, or transdermal hormonal contraception)
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)

Additional effective contraceptive methods include the following:

- Male latex or synthetic condom
- Diaphragm
- Cervical cap

Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of childbearing potential while taking lenalidomide and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy.

5.3. Enrollment

All screening procedures must be performed within 28 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.

5.3.1. Patient Numbering

After obtaining informed consent, a unique patient number will be assigned to the potential study participant by sponsor medical monitor. A patient number will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

5.3.2. Medical and Cancer History

Background information to be collected includes history of disease (including the date of initial diagnosis and current disease status), staging, sites of disease, and presence or absence of disease-related constitutional symptoms. Prior medications/significant non-drug therapies and demographic data (gender, year of birth [or age] and race/ethnicity) will also be collected.

5.3.3. Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria should be met. No eligibility waiver will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet, and the medical monitor or designee provides final approval for enrollment in writing. Study site personnel should ensure that a medical monitor–approved Eligibility Packet is in the patient's file before proceeding with study procedures.

5.3.4. Enrollment

After a patient has been approved by the medical monitor or designee to enroll in the study, study treatment must commence within 5 days after enrollment.

5.4. Safety Assessments

5.4.1. Physical examination and Vital signs

Physical examination, and weight will be performed at screening, Day 1 of each cycle and Safety follow-up visit. Height (cm) is determined at screening only. A complete physical examination includes an assessment of systems per standard of care at the study site and as clinically indicated by symptoms. Vital signs (sitting blood pressure, pulse, and body temperature) will be performed after the patient has rested in the sitting position for ≥3 minutes at screening visit, each visit during study treatment and Safety follow-up visit.

5.4.2. ECOG performance status

ECOG performance status will be assessed at screening visit, each visit during study treatment and Safety follow-up visit.

5.4.3. 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 obtaining the ECGs.

5.4.4. Echocardiogram

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

5.4.5. Adverse Events Review

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

Collect non-serious AE information from the time of first dose of study drug to 30 days after the last dose of zanubrutinib or lenalidomide, whichever occurs later. Information on all SAEs (regardless of relatedness) will be collected from the time of signing of informed consent to screen failure or to 30 days after the last dose of zanubrutinib or lenalidomide, whichever occurs later. The AE reporting period is defined in Section 8.3.1.

The accepted regulatory definition for an AE is provided in Section 8.1.1 and the definition of an SAE is provided in Section 8.2.1. Important additional requirements for reporting SAEs are explained in Section 8.

5.5. Efficacy Assessments

Response will be assessed per the Lugano Classification. The secondary endpoint for Part 1 and the primary endpoint for Part 2 is ORR, defined as the achievement of either PR or CR according to the Lugano Classification (Cheson 2014) at any time on study drug. Response parameters will include assessment of lymphadenopathy, organomegaly, and bone marrow examination. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 6).

5.5.1. Radiographic Imaging

CT with contrast unless contraindicated of neck, chest, abdomen, and pelvis will be performed at screening, every 12 weeks for the first 48 weeks, every 16 weeks for the next 48 weeks, and every 24 weeks thereafter until disease progression, use of alternative anti-cancer therapy until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.

A magnetic resonance image (MRI) may be used in place of CT only for patients who cannot undergo CT due to contrast allergy. 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.

5.5.2. Positron Emission Tomography

A PET/CT scan or PET scan will be performed at screening. For patients with PET-avid disease at screening, PET scans will also be performed at the same visits as CT scan. An assessment of CR must be confirmed by PET scan.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast.

If using a hybrid machine to acquire both PET and CT, the PET must be performed before the CT with IV contrast as to not compromise PET results. If independent CT and PET scanners are used, and the patient is receiving both scans on the same day, the PET must be performed before the CT with IV contrast.

5.5.3. Bone Marrow Aspiration/Biopsy

A unilateral bone marrow aspiration and biopsy must be performed at screening if not performed within 60 days before the first dose for all patients, provided it is performed as part of their standard care and there has been no intervening therapy between the time of the biopsy and start of study drug. In those patients who had evidence of bone marrow disease at screening, upon achieving a possible CR (eg, physical examination or imagine indicating a possible CR), a bone marrow aspiration and biopsy should be obtained to confirm the CR.

5.6. Pharmacokinetics

5.6.1. Part 1

Blood will be collected to characterize the PK profile of zanubrutinib and lenalidomide after single dose and at steady state. Blood samples (4 mL) will be collected into EDTA collection tubes from all patients of dose escalation after the morning dose at the timepoints shown in Table 2. Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Lab Manual for this study.

On Cycle 1 Day 1 and Cycle 1 Day 21, patients will receive oral dosing of zanubrutinib and lenalidomide at the clinic, and dosing time and PK collection time will be collected on electronic case report form (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 Cycle 1 Day 21.

Table 2: Pharmacokinetic Sampling in Part 1

Procedure	**Cycle 1 Day 1**						
Hours	Predose (-30 min)	0.5 (± 10 min)	1 (± 10 min)	2 (± 10 min)	3 (± 15 min)	4 (± 15 min)	8 (± 30 min)
Pharmacokinetics blood sampling	X	X	X	X	X	X	X
Procedure	**Cycle 1 Day 21**						
Hours	Predose (-30 min)	0.5 (± 10 min)	1 (± 10 min)	2 (± 10 min)	3 (± 15 min)	4 (± 15 min)	8 (± 30 min)
Pharmacokinetics blood sampling	X	X	X	X	X	X	X

Additional PK samples may be taken if needed, to further evaluate zanubrutinib and lenalidomide exposure. The investigator will record the time of blood collection and the time of administration in the eCRF.

5.6.2. Part 2

Blood will be collected to characterize the PK profile of zanubrutinib and lenalidomide after single dose and at steady state. Blood samples (4 mL) for PK analysis will be collected into EDTA collection tubes after the morning dose at the timepoints shown in Table 2 (same as Part 1).

On Cycle 1 Day 1 and Cycle 1 Day 21, patients will receive oral dosing of zanubrutinib and lenalidomide at the clinic and dosing time and PK collection time will be collected on 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 Cycle 1 Day 21.

PK blood sampling for zanubrutinib and lenalidomide will be performed for twelve patients from the first stage enrollment. The PK sample size and sampling timepoints may be modified based on PK results of Part 1. Details concerning handling of the PK plasma samples, including labeling and shipping instructions, will be provided in the Laboratory Manual for this study.

5.7. Laboratory Assessments

Laboratory assessments should be performed at a local certified laboratory.

Chemistry, complete blood count (CBC), coagulation, urinalysis, serum immunoglobins, hepatitis serologies, and thyroid function will be performed at the timepoints specified in the Schedule of Assessments (Appendix 6) and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first dose of study drug.

Screening tests (including CBC, chemistry and coagulation) performed within 72 hours of the first study drug administration do not need to be repeated in Cycle 1. Screening hepatitis serologies performed within 4 weeks before the first study drug administration do not need to be repeated in Cycle 1.

5.7.1. Urinalysis

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

5.7.2. Hematology

Hematology assessments (which include hemoglobin, hematocrit, platelets, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils and basophils) are required to be performed at Screening, every visit during the treatment phase and Safety follow-up visit (if necessary, as defined in Section 5.11).

5.7.3. Chemistry

Chemistry assessments include sodium, potassium, chloride, urea or blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate or phosphorus, uric acid, magnesium and bicarbonate (or CO_2 combining performance, CO_2CP). Chemistry assessments will be performed at screening, at Cycle 1, weekly on Day 1 of subsequent cycles and Safety follow-up visit (if necessary, as defined in Section 5.11).

5.7.4. Coagulation Profile

The coagulation profile includes prothrombin time (which will also be reported as international normalized ratio) and activated partial thromboplastin time. The coagulation profile will be performed at screening, Day 1 of subsequent cycles and Safety follow-up visit.

5.7.5. Thyroid function

Thyroid stimulating hormone (TSH) will be used to evaluate thyroid function. If abnormal, further testing should be performed as clinically appropriate. Testing will be performed at Screening and at the Safety follow-up visit. Testing at additional timepoints may be performed at the Investigator's discretion.

5.7.6. Serum immunoglobulins

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

5.7.7. Hepatitis Serology

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

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

If, during monthly monitoring of HBV DNA by PCR, the value is between 20 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 positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, 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.

Section 4.2 describes how the results for HBV and HCV testing at Screening relate to study eligibility.

5.7.8. Pregnancy Test

Two negative pregnancy tests must be obtained for all women of childbearing potential before initiating therapy. The first test must be performed within 10-14 days before lenalidomide therapy and the second test within 24 hours before lenalidomide therapy. At least one test should be a blood pregnancy test.

Urine pregnancy tests will be performed weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy tests must be continued every 4 weeks (cycle) for at least 90 days after the last dose of zanubrutinib and lenalidomide, whichever comes last. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

5.8. Biomarker Assessments

Tissue and blood samples for biomarker assessment will be collected as stated in Appendix 6. Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the Laboratory Manual for details of sample handling.

No less than 15 unstained slides must be sent to the central laboratory for biomarker analysis including assessments of DLBCL subtype by both IHC and GEP methods, EBV infection status, MYC/BCL2/BCL6 rearrangement or expression status, TCL1A expression status, Ki67 and other protein expression related to disease or treatment mechanism, presence of immune cells in tumor microenvironment assessment, genetic alterations, gene expression and proteomics, etc.

The archival tumor tissues are mandatory for all patients who consent to participate in the study, although a fresh baseline tumor biopsy is strongly recommended. If no archival samples are available, a fresh tumor biopsy collected at screening is required. For these patients, an optional biopsy for biomarker analysis after approximately 3 cycles of treatment is strongly recommended. 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. Enrollment of 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.

Optional biopsy will also be taken from the patients who have confirmed disease progression during the study at accessible tumor sites to explore resistance mechanism. Drug resistance -associated genetic alterations, gene expressions, and presence of immune cells in tumor microenvironment will be determined. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Blood samples will be collected at screening, scheduled response assessment visits, and at unscheduled visits when disease progression is to be confirmed. Blood-based biomarker analysis such as DNA/ctDNA sequencing, GEP, cfDNA assessment, immune cell and cytokine profiling, plasma protein, etc will be performed to explore their association with response, resistance and prognosis.

5.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include vital signs/focused physical examination, ECOG performance status, AE review, concomitant medications and procedures review, radiographic assessments, physical examination, disease-related constitutional symptoms, and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

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

5.10. End of Treatment Period

The treatment period starts with the first day of assigned study treatment and ends 30 days after date of permanent study drug discontinuation (30 days after the final administered dose of zanubrutinib or lenalidomide, whichever is later).

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

- Pregnancy
- Disease progression
- AE(s)
- Patient withdraw consent
- Investigator decision
- Other

5.11. 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 study drug (zanubrutinib or lenalidomide, whichever is later) or before the start of a new anticancer treatment, whichever occurs first, to collect AEs, including AEs that may have occurred or been ongoing after the patient discontinued study treatment. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information.

All adverse events, including SAEs, will be collected as described in Section 8.

5.12. Follow-up Phase

Once a patient has completed the Safety follow-up visit, he/she will enter the Follow-Up Phase. Patients who withdraw from treatment for reasons other than PD will participate in ongoing Response Follow-Up.

5.12.1. Response Follow-up

Patients who discontinue the study treatment for reasons other than PD continue to be followed for efficacy evaluations per protocol schedule until patient exhibits first progression, starts new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. During this period, CT/MRI and PET scans will be done per Investigator discretion.

5.12.2. Long-term Follow-up

Once patients progress or start use of alternative anticancer therapy (for patients who have not withdrawn consent), they will be contacted approximately every 3 months (±14 days) by telephone to assess survival and the use of alternative anticancer therapy. Patients will be contacted until death, patient withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

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

5.13. End of Study

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

- Patient withdrew consent
- Death
- Study termination by sponsor
- Other

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

The end of the study is defined as the last visit (the safety follow-up contact) of the last patient undergoing study treatment on this protocol or the last patient undergoing study treatment has been transitioned onto an extension study.

5.14. Lost to Follow-up

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

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

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

6. STUDY TREATMENT

6.1. Zanubrutinib

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

6.1.1. Packaging and Labeling

The capsule supplied for zanubrutinib will be provided in a child-resistant, high-density, polyethylene bottle with induction seal and bottle label. Labels will be prepared in accordance with Good Manufacturing Practices (GMP) and local regulatory guidelines of the participating country. Label text will be translated into local language as required. The contents of the label will be in accordance with all applicable local regulatory requirements.

6.1.2. Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug specific requirements. The study drugs must be kept at the temperature condition as specified on the labels.

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

6.1.3. Compliance and Accountability

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

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

6.1.4. Disposal and Destruction

At appropriate times during the conduct of the study or at the end of the study 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

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 on the appropriate eCRF.

Zanubrutinib will be administered as two 80-mg capsules orally twice daily (160 mg twice daily) 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.

Zanubrutinib dosing is continuous (without interruption) throughout the treatment phase. If Day 1 lenalidomide dosing is delayed for toxicity that does not require zanubrutinib to be held for toxicity, dosing of zanubrutinib should continue.

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. AEs associated with an overdose of study drug will be recorded on the adverse event eCRF. Any SAEs associated with an overdose are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.5.1. There is no specific antidote for zanubrutinib overdose. In an 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 upon the type of surgery and the risk of bleeding.

6.1.7. Dose Interruption and Modification

The guidelines in Table 3 should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.1.7.1) and non-hematologic 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 medical monitor.

6.1.7.1. Dose Reduction for Hematologic Toxicity

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

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

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. If the same event recurs, patients will restart at 1 dose level lower (level -1) upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions will be allowed.

Patients with ≥ Grade 3 thrombocytopenia associated with significant bleed requiring medical intervention will be discontinued from study treatment.

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

6.1.7.2. Dose Reduction for Non-Hematologic Toxicity

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

If the event recurs at ≥ Grade 3, study drug will be held until recovery to ≤ Grade 1 or baseline, then restart at 1 dose level lower (level -1). If the event recurs at ≥ Grade 3 at level -1, drug will be held until recovery to ≤ Grade 1 or baseline, then restart at level -2. If the event recurs at ≥ Grade 3 at level -2, the patient will be discontinued from study treatment.

For patients with symptomatic and/or incompletely controlled ≥ Grade 3 atrial fibrillation, study drug may be restarted at either the original dose or at dose level -1 atrial fibrillation is controlled at the discretion of the treating investigator.

Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.7.7.

6.2. Lenalidomide

All patients of this study will receive lenalidomide and will follow guidelines for lenalidomide dosing and toxicity management.

6.2.1. Formulation, Packaging, and Storage of Lenalidomide

Lenalidomide (Revlimid®) will be supplied as capsules for oral administration by sponsor.

Lenalidomide will be shipped to the pharmacy at the study site in individual blister packs. Blister packs will contain sufficient capsules to last for one cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible.

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

Lenalidomide should be stored at the temperature conditions as specified on the label.

6.2.2. Dosage, Preparation and Administration of Lenalidomide

The first dose of lenalidomide will be administered orally on Cycle 1 Day 1, of the Treatment Phase, after which lenalidomide will be self-administered daily by the patients on Days 1-21 of each cycle.

Lenalidomide will be dosed at the same time as zanubrutinib.

Lenalidomide should be administered with water. The capsule should be swallowed intact and patients should not attempt to chew capsules, open capsules, or dissolve them in water. Each dose of lenalidomide should be taken with or without food, at approximately the same time each day.

Females of childbearing potential are suggested not to handle or administer lenalidomide unless they are wearing gloves.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If a dose is missed for the entire day, it should not be made up.

Lenalidomide dosing during the Treatment Phase occurs on Days 1-21 each cycle followed by a mandatory 7-day drug-free interval. If a Day 1 (of any Cycle) is delayed due to scheduling, instruct the patient that lenalidomide dosing should not be initiated until Day 1 assessments can occur.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 5.10 .

Dose modifications for toxicity are outlined in Section 6.2.4, Table 4 and Table 5. For instructions regarding drug accountability and disposal/return of unused lenalidomide refer to the Pharmacy Manual.

6.2.3. Dose Delay, Reduction or Discontinuation of Lenalidomide

In order to initiate a new cycle of therapy with lenalidomide, the patient must have an ANC ≥1,000/μL and a platelet count ≥50,000/μL and no lenalidomide-related ≥ Grade 3 toxicity on Day 1. If these two criteria are not met, a repeat assessment is to be performed per the Investigator's decision. The initiation of lenalidomide should be delayed until the patient meets the above criteria at which time the patient will initiate drug without dose modification. The initiation of lenalidomide may occur on any day of the cycle but missed doses must be omitted. Omitted doses should not be made up, and lenalidomide dosing must end no later than Day 21 of any given cycle. Once a cycle has initiated, if lenalidomide must be held for toxicity during dosing, lenalidomide will not resume until Day 1 of the subsequent cycle, provided the patient meets the cycle initiation criteria above, with dose adjustments as per Table 4.

Treatment with lenalidomide should be withheld for any unmanageable, potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity as described in Table 4. In the event the patient is diagnosed with a thyroid condition or experiences a drop in creatinine clearance to ≤60 mL/min, refer to Table 4 for further instructions.

Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the Medical Monitor.

Lenalidomide may be withheld for a maximum of 28 consecutive days for toxicity.

Lenalidomide treatment should be discontinued in the event of a lenalidomide related toxicity lasting more than 28 days, unless approved by the Medical Monitor.

6.2.4. Dose Modification of Lenalidomide during a Cycle (Applies to Days 1-21)

The dose of lenalidomide should be modified according to the dose modification guidelines in Table 4 based on investigator assessment of lenalidomide relatedness if any of the following toxicities occur:

Table 4: Dose Modification or Interruption for Lenalidomide Toxicity during a Cycle

Toxicity	Intervention
Thrombocytopenia: • Grade 3 (decrease to <50,000/μL) associated with ≥ Grade 2 bleeding, OR • Grade 4 (decrease to <25,000/μL)	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 6.2.3). Do not dose below 5 mg daily.
Neutropenia: • ANC <1,000/μL for > 7 days, OR • ANC <1,000/μL with an associated temperature ≥38.5°C, OR ANC <500/μL	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 6.2.3). Do not dose below 5 mg daily.
Rash: • Any Grade desquamating (blistering) • Grade 4 non-blistering	• Discontinue lenalidomide permanently
Venous thromboembolism (VTE) ≥ Grade 3	• Interrupt lenalidomide treatment for the remainder of the cycle • Initiate VTE treatment • Resume lenalidomide without dose modification at the start of the next cycle if the benefit of therapy on this study outweighs the risk for bleeding.
Hyperthyroidism or hypothyroidism	• Interrupt lenalidomide treatment for the remainder of the cycle • Evaluate etiology and initiate appropriate therapy • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 6.2.3). Do not dose below 5 mg daily.

Toxicity	Intervention
Creatinine Clearance <60 mL/min (Cockcroft-Gault)	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide according to the recommendations below based upon creatinine clearance at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 6.2.3). Do not dose below 5 mg daily. o Creatine clearance (CrCl) 30-60 mL/min: 10 mg every 24 hours o CrCl <30 mL/min (not requiring dialysis): 15 mg every 48 hours • If creatinine clearance becomes ≥60 mL/min for a minimum of 2 cycles then one may re-escalate to the dose before reduction for renal dysfunction at the discretion of the investigator.
Any other Grade 3 or 4 non-hematologic toxicities attributed to lenalidomide	• Interrupt lenalidomide treatment for the remainder of the cycle. • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 6.2.3). Do not dose below 5 mg daily.

Table 5: Dose Reduction of Lenalidomide

Current Dose Level	15 mg	20 mg	25 mg
Dose Reduction 1	10 mg	15 mg	20 mg
Dose Reduction 2	5 mg	10 mg	15 mg
Dose Reduction 3	Discontinue	5 mg	10 mg
Dose Reduction 4	NA	Discontinue	5 mg
Dose Reduction 5	NA	NA	Discontinue

6.2.5. Overdose

There is no specific experience in the management of lenalidomide overdose in patients; although in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

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 on the eCRF and in the patient's source documents.

All prior therapies for DLBCL, including immunochemotherapy, chemotherapy, transplant, targeted therapy, radiation therapy, etc. will be recorded on the eCRF with the 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 or lenalidomide, whichever occurs later) 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 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 of corticosteroids (at doses ≤20 mg/day prednisone equivalent) given with antineoplastic intent is allowed within 7 days prior the first dose of study drug
  - Chronic systemic corticosteroid use is not permitted, except for adrenal replacement, and requires consultation with the medical monitor.
- Therapy to reduce symptoms per standard of care and institutional guidelines

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

7.2.2. Prohibited Medications

Patients should not receive other anti-cancer therapy (eg, chemotherapy, biologics, or immunotherapy) while on treatment in this study.

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

7.3.1. CYP-Inhibiting/Inducing Drugs

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 4 for a list of these medications) and grapefruit juice and Seville oranges should be done with caution, as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table in Appendix 3. The medical monitor should be consulted in these situations. Please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers List (FDA 2019) for a more complete list.

Clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Since blood levels and 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, a second barrier method of contraception (eg, condoms) is recommended to be used. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

Lenalidomide has a low potential for pharmacokinetic drug interactions. But periodic monitoring of digoxin concentration is recommended in accordance with clinical judgement and based on standard clinical practice during therapy since the digoxin C_{max} and AUC_{inf} were increased by 14% when digoxin was co-administered with lenalidomide. Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients. For detail information of lenalidomide investigators could consult the relevant prescribing information and Summary of Product Characteristics.

8. SAFETY MONITORING AND REPORTING

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

8.1. Adverse Events

8.1.1. Definitions

An AE is defined as any untoward medical occurrence in a patient temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (zanubrutinib in combination with lenalidomide).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Examples of an AE include:

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

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

8.1.1.1. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0

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 non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living

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

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

8.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Prescribing Information, for marketed products, in the determination of his/her assessment.

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

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

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

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

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

8.1.1.3. Follow-Up of Adverse Events and Serious Adverse Events

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.5.1.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, or coagulation) or other abnormal assessments (eg, ECG, radiographical studies, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worsen will not be reported as AEs or SAEs. The definition of clinically significant is left to the judgment of the investigator; in general, these are events that result in clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, require close observation, more frequency follow-up assessments or further diagnostic investigation.

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

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C, see Section 5.7.7.

8.1.3. Lack of Efficacy

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

8.2. Serious Adverse Events

8.2.1. Definitions

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

- Results in death.
- Is life threatening.

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

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

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

The following are NOT considered SAEs:

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

8.2.2. 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 current protocol and/or Investigator's Brochure.

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

8.3.1. Adverse Event Reporting Period

After informed consent has been signed but before the administration of the study drug, only SAEs should be reported to the sponsor. Any arising or worsening condition experienced by the patient after signing the informed consent but before first dose of study drug that does not meet the definition of serious should be reported only as medical history.

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

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

8.3.2. Eliciting Adverse Events

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

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

8.3.3. Disease Progression

Disease progression which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression".

8.3.4. 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 unknow cause", or "death unexplained".

8.4. Safety Monitoring Committee

All enrolled patients will be evaluated clinically and with standard laboratory tests during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events (AEs), physical examinations, and laboratory measurements (hematology, chemistry, and urinalysis).

Patients will be evaluated for AEs (all grades, according to NCI-CTCAE v5.0) and serious adverse events (SAEs). Patients who have an AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

A SMC will monitor safety data periodically throughout the study. As the efficacy endpoints require longer length of follow-up to be adequately evaluated, a formal interim review of data collected during the study by the SMC will focus on the safety aspects of the study. The SMC will evaluate safety data from the dose escalation potion (Part 1) and decide the dose level for next group or if enroll more eligible patients, based on the safety data from the former dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed. No recruitment stop is planned for this interim safety review for Part 2. At the safety review, special attention will be paid to significant safety events (SSE). Subsequent safety data review is outlined in SMC charter.

An SSE is defined as any of the following:

- General toxicity (NCI-CTCAE v5.0): Grade 3 and Grade 4 AEs and SAEs
- Any adverse event that requires dose interruption, reduction or discontinuation of the study drug.
- A patient's death

In the case of major toxicity concerns, the SMC can recommend modifying the study conduct.

8.5. Prompt Reporting of Serious Adverse Events

8.5.1. Time Frames for Submitting Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 6.

Table 6: Time Frame for Reporting SAEs to the Sponsor or Designee

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

Abbreviations: AE, adverse event; SAE, serious adverse event.

8.5.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 8.5.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 8.1.1.2.

The sponsor will provide contact information for SAE receipt.

8.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.5.2. 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 SAEs to regulatory authorities and the IRB/IEC.

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

8.6. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 90 days of the last dose of zanubrutinib or lenalidomide, whichever comes last, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

8.7. Recording Poststudy Adverse Events

A poststudy AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.3.1.

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

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

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

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

- Zanubrutinib Investigator's Brochure
- Prescribing information for lenalidomide

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Study Endpoints

9.1.1. Part 1

9.1.1.1. Primary Endpoint

The primary endpoint is the safety of zanubrutinib combined with lenalidomide. It will be assessed throughout the study by monitoring AEs and SAEs, per the NCI-CTCAE v5.0, physical examination and laboratory measurements.

The RP2D of lenalidomide will be determined based on safety data.

9.1.1.2. Secondary Endpoints

Define the best overall response (BOR) as the best response recorded from the start of the combination therapy until data cut or start of new anti-neoplastic treatment.

The secondary endpoints are:

- ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification (Cheson 2014).
- PK evaluations for zanubrutinib and lenalidomide, as appropriate and allowed by the data:
  - Single dose: including but not limited to $AUC_{(0\text{-}t)}$, C_{max}, T_{max}, CL/F.
  - Steady state: including but not limited to $AUC_{(0\text{-}t)}$, $C_{max,ss}$, T_{max}, C_{trough}, CL/F, Ro.
- Clinical outcomes, as measured by ORR, based on the GCB and non-GCB identified by IHC and ABC and GCB subtype identified by GEP.

9.1.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Efficacy endpoints of zanubrutinib combined with lenalidomide, including CRR, DOR, PFS, TTR and OS, in the efficacy analysis set as well as the subgroups classified by IHC and by GEP. Exploratory efficacy endpoints as determined by investigator are as follows:
  - CRR, defined as the proportion of patients whose BORs are CR based on the Lugano classification (Cheson 2014).

  - DOR, defined as the time from the first response documentation to the date that progression is documented after treatment initiation or death, whichever occurs first.
  - PFS, defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first
  - TTR, defined as the time from treatment initiation to the first documentation of response.
  - OS, defined as the time from treatment initiation until death.
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR, OS) by clinical/genetic risk factors.
- Potential resistance biomarkers and mechanisms of resistance.

9.1.2. Part 2

9.1.2.1. Primary Endpoint

The primary endpoint of Part 2 of this study is the ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification (Cheson 2014).

9.1.2.2. Secondary Endpoint

- Clinical outcomes of zanubrutinib combined with lenalidomide, as determined by investigators, including CRR, DOR, PFS and TTR, in the efficacy analysis set as well as the subgroups classified by IHC and by GEP.
- The safety and tolerability of zanubrutinib combined with lenalidomide will be assessed throughout the study by monitoring AEs and SAEs, per the NCI-CTCAE v5.0, physical examination and laboratory measurements.
- PK evaluations for zanubrutinib and lenalidomide, as appropriate and allowed by the data:
  - Single dose: including but not limited to $AUC_{(0-t)}$, C_{max}, T_{max}, CL/F.
  - Steady state: including but not limited to $AUC_{(0-t)}$, $C_{max,ss}$, T_{max}, C_{trough}, CL/F, Ro.
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR) based on the GCB and non-GCB identified by IHC and ABC and GCB subtype identified by GEP.

9.1.2.3. Exploratory Endpoints

- OS
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR and OS) by clinical/genetic risk factors.
- Potential resistance biomarkers and mechanisms of resistance.

9.2. Statistical Analysis

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

9.2.1. Analysis Sets

Safety analysis set is defined as all patients who are exposed to at least one dose of any medication within the combination therapy.

Efficacy analysis set is defined as all patients who are exposed to at least one dose of any medication with confirmed R/R DLBCL. Patients with no post-baseline response assessments will be treated as non-responders. It will be used as the primary analysis set for all the efficacy analyses.

Efficacy evaluable analysis set is defined as all patients who are exposed to at least one dose of any medication with confirmed R/R DLBCL and have at least one post-baseline response assessment unless discontinued treatment due to clinical progression or death prior to response assessment in the efficacy analysis set. It will be used for sensitivity analyses.

All patients who have at least one postdose plasma concentration and no major protocol deviation affecting PK would be included in the PK analysis set.

Major protocol deviations will be summarized and listed by each category.

9.2.2. Patient Disposition

The number of patients enrolled, treated, and discontinued from study drug or 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 cut-off date will be summarized using the data from the eCRF.

9.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized. Continuous variables include age, weight, vital signs, time since initial DLBCL diagnosis; categorical variables include sex, age group, disease stage, ECOG-PS, prior line of therapy for DLBCL, IPI, EBV and Ki67, subtype of GCB, non-GCB and ABC.

9.2.4. Prior and Concomitant Therapy

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. Prior medications will be defined as medications that started 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, or lenalidomide, whichever occurs later.

9.3. Efficacy Analyses

9.3.1. Hypothesis Test

No hypothesis testing will be done for Part 1.

In Part 2, the ORR with the combination therapy is estimated as 55% in the overall R/R DLBCL patient population, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: ORR=25%

Ha: ORR > 25%

A binomial exact test will be performed for hypothesis testing H0: ORR=25% vs. Ha: ORR > 25% in the efficacy analysis set. If 15 or more responses are observed in 36 patients, then the historical control rate of 25% can be ruled out at one-sided alpha of 0.025. Therefore, the superiority of the combination therapy will be demonstrated.

As stated in the study design, for Part 2, Simon's two-stage design will be used. If within the first 18 patients in Part 2, 4 or fewer responses are observed, the study will be stopped.

9.3.2. Efficacy Analysis for Categorical Endpoints

ORR, defined as the achievement of either a PR or CR in the best overall response (BOR) at any time on study drug. BOR is defined as the best response recorded from the start of the combination therapy until data cut or start of new anti-neoplastic treatment. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR.

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the ORR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented.

9.3.3. Efficacy Analysis for Time to Event Endpoints

PFS is defined as the time from the starting date of the combination 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 tumor assessment.

Kaplan-Meier method will be used to estimate progression event-free curves and corresponding quantiles (including the median). A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. The PFS 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.

The PFS censoring rule will follow FDA Guidance for Industry Clinical Study Endpoints for the Approval of Cancer Drugs and Biologics (2007).

TTR is defined as time from the starting date of combination therapy to the date the response criteria are first met. Patients who do not have response will be censored at their last valid assessment.

DOR 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. Patients who do not have disease progression will be censored at their last valid assessment.

OS is defined as the time from the starting date of the combination 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.

Time to event endpoints (DOR, TTR and OS) will be similarly analyzed using the Kaplan-Meier method as described above for PFS. The Kaplan-Meier estimates of TTR, DOR and OS will be plotted over time.

9.3.4. Biomarker Analyses

9.3.4.1. Predictive biomarkers

The primary predictive biomarker analysis is based on a subset of the patients with both a valid subtype classification measured by IHC and/or GEP, and at least one disease assessment post-treatment. Clinical outcomes (ORR, CRR, DOR, PFS, TTR) will be analyzed in subgroups identified by these biomarker subtypes (ie, GCB, non-GCB, ABC or unclassified) using the same methods described in Section 9.3.

A supportive analysis is based on patients with a valid subtype classification measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response. Similar analyses described above will also be used.

Other statistical models (ie, logistic model for ORR, or Cox's proportional model for time to event endpoints) may be explored with biomarker subtype index as covariate to explore the correlation between the two variables.

Exploratory analyses of other predictive biomarkers or clinical/genetic risk factors such as Ki67, EBV infection status, MYC/BCL2/BCL6 rearrangement status, genomic alteration status, tumor infiltrating lymphocytes (TIL) levels, etc will be conducted similarly if data is available.

9.3.4.2. Other biomarkers

For patients with paired tumor biopsies or blood, correlation between changes in the tumor tissues or peripheral blood, including but not limited to BTK pathway gene expression, TIL levels, RNA expression and DNA mutational profiling, immune cell and cytokine profiling, ctDNA levels, and tumor response will be analyzed to identify potential pharmacodynamics and monitoring biomarkers.

When deemed necessary, correlation analyses described for the predictive biomarkers will also be performed for these pharmacodynamics and monitoring biomarkers versus clinical outcomes. These biomarkers may be treated as continuous and/or categorical variables (if suitable threshold can be identified) in these analyses.

Tumor biopsy and blood samples taken at disease progression or response during the study will be used to identify potential resistance biomarkers to study mechanisms of resistance. Similar analyses described for above monitoring biomarker will also be performed for these resistance biomarkers, by replacing the efficacy endpoint of the response status with progression status.

9.3.5. Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: sex, age group (≥60), disease stage, disease status (relapsed vs. refractory), ECOG-PS (0 vs. ≥1), number of prior lines of therapy, IPI, bulky disease (>7.5 cm). Within group values (rates or means/medians) will be presented in forest plots.

9.4. Safety Analyses

The sponsor, leading investigator and maybe other investigators will establish a SMC for ongoing safety assessment throughout the study. The SMC charter will define the organization members and procedures. The SMC will evaluate safety data from the dose escalation potion (Part 1) and decide the dose level for next group or if enroll more eligible patients, based on the safety data from the former dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed.

Patients will be evaluated for AEs (all grades, according to NCI-CTCAE v5.0) and serious adverse events (SAEs). Patients who have an AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

9.4.1. 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 AEs 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.

9.4.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized preferred terms (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher.

A treatment-emergent AE (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib or lenalidomide (whichever comes later), or the start of new anti-cancer therapy, whichever comes first. Worsening of an event to Grade 5 beyond day 30 after last dose of study drug is also considered a TEAE (if it is prior to new anticancer therapy start). Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (and percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade according to NCI-CTCAE v5.0 within a SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. Serious AEs, deaths, TEAEs ≥ Grade 3, treatment-related AEs, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption, will be summarized.

9.4.3. Laboratory Analyses

Clinical laboratory (ie, hematology, serum chemistry, 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 CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

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

9.4.4. Vital Signs

Vital signs (actual value and change from baseline), including systolic and diastolic blood pressure, pulse, temperature, and weight, will be summarized by visit.

9.5. Pharmacokinetic Analyses

Plasma zanubrutinib and lenalidomide concentration time data will be summarized and displayed in both tabular and graphical form. Individual and mean plasma concentration versus time data will be tabulated and plotted by dose level.

The PK parameters will be estimated based on non-compartmental analysis methods and will be computed using Phoenix WinNonlin® Version 7.0.

The PK parameter estimates for a single dose profile includes but is not limited to the following:

- $AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve from zero to the last measurable concentration
- C_{max}: Maximum plasma concentration
- T_{max}: Time to maximum plasma concentration
- CL/F: Apparent clearance, calculated as dose/$AUC_{0\text{-}t}$

The PK parameter estimates following multiple doses included but not limited to the following:

- $AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve from zero to the last measurable concentration
- $C_{max,ss}$: Maximum plasma concentration at steady state
- T_{max}: Time to maximum plasma concentration
- C_{trough}: Minimal drug concentration (trough) at steady state
- Ro: Accumulation ratio (R_{AUC}: AUC on Day 21 of Cycle 1/AUC on Day 1 of Cycle 1, R_{Cmax}: C_{max} on Day 21 of Cycle 1/C_{max} on Day 1 of Cycle 1)
- CL/F: Apparent clearance, calculated as dose/$AUC_{0\text{-}t}$

These and additional PK parameters will be calculated if deemed appropriate and allowed by the data.

Estimates for these parameters will be tabulated and summarized by the dose level, schedule, and collection day (ie, sample size, mean, standard deviation, inter-patient variability (CV%), median, min, and max, geometric mean and geometric CV%).

Possible drug-drug interactions between zanubrutinib and lenalidomide may be evaluated as exploratory analysis by comparison of the pharmacokinetic data generated in the present study and historical data.

9.6. Sample Size Determination

The number of dose levels examined and the emerging toxicities of the combination therapy will determine the sample size. It is anticipated that approximately 27 patients in Part 1 and approximately 36 patients in Part 2 will be required. With about 10% dropout rate for Part 2, approximately 67 patients will be enrolled.

Sample size for Part 1 will depend on the number of dose levels examined and the emerging toxicities of the combination therapy. It is expected the maximum of patients in Part 1 will not exceed 27 patients.

For Part 2, Simon's two-stage design (Simon 1989) will be used. The null hypothesis that the true response rate is 0.25 will be tested against a one-sided alternative. In the first stage, if there are 4 or fewer responses in these 18 patients, the study will be stopped. The null hypothesis will be rejected if 15 or more responses are observed in 36 patients. This design yields a type I error rate of 0.025 and power of 96% when the true response rate is 0.55.

9.7. Interim Analysis

For Part 2 , one futility interim analysis will be conducted based on the Simon 2-stage design (see Section 9.6 for details).

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

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

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

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

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

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

11.2.2. Ethical Conduct of the Study and Ethics Approval

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

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate 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 informed consent form, and any other information that the IRB/IEC has approved for presentation to potential patients.

If the protocol, the informed consent form, or any other information that the IRB/IEC has approved for presentation to potential patients is amended during the study, the investigator (or sponsor, where applicable) 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 informed consent form 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 informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

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

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

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.5.3, the investigator (or sponsor, where applicable) is responsible for reporting SAEs 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

Information on maintaining patient confidentiality and privacy in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent form process, either as part of the informed consent form or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient age, date of independent central review, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

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

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

11.2.6. Data Collection

Data required by the protocol will be entered into an 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 must sign the completed casebooks to attest to their 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.

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

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

11.2.8. Drug Accountability

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensing records will document quantities received from BeiGene, quantities dispensed to patients, and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, 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, after 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 periodically reviewed and verified by the study monitor over the course of the study.

11.2.9. Inspections

The investigator should understand that the facilities used for this study and all 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.

11.2.10. Protocol Adherence

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

11.2.11. Financial Disclosure

Investigators are required to provide the sponsor with sufficient, accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

11.2.12. 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 informed consent form 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 informed consent form confirming willingness to remain in the study.

11.3. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International 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 2013).

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

11.4. Study and Study Center Closure

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

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

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 any reason including, but not limited to, safety or ethical issues or severe noncompliance with this protocol, Good Clinical Practice, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before 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 still be provided to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

11.5. Records Retention and Study Files

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

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

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

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

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

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

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

Biological samples remaining after this study may be retained in storage by the sponsor for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

11.6. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor. Use of the provided study drug for purposes other than this study is strictly prohibited and any data or property rights generated are forfeit and the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during 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 that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

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

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB 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 which may be published as described in Section 11.3.

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

11.7. Joint Investigator/Sponsor Responsibilities

11.7.1. Access to Information for Monitoring

In accordance with International Council on Harmonisation Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation 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 during these monitoring visits are resolved.

11.7.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to 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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APPENDIX 1. THE LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3* with or without a residual mass on 5PS▪ It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra-lymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement♦	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology (if BMA involved at screening), if indeterminate, IHC negative
Partial	Partial metabolic response:	Partial remission (all of the following):
Lymph nodes and extra-lymphatic sites	Score 4 or 5▪ with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 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
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

Response and Site	PET-CT-Based Response	CT-Based Response
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
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5▪ with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following:
Individual target nodes/nodal masses	Score 4 or 5▪ with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	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 1.0 cm for lesions > 2 cm

Response and Site	PET-CT-Based Response	CT-Based Response
Non-measured lesions	None	New lesions or clear progression of pre-existing non-measured lesions: • 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
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	
Organ enlargement	Not applicable	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
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; BMA, bone marrow assessment; CT, computed tomography; FDG, F-fluoro-2-deoxy-d-glucose; IHC, immunohistochemistry; LDi, longest diameter; PET, positron emission tomography; PPD, product of the perpendicular diameters; SDi, shortest diameter; SPD, sum of the products of diameters.
Source: Cheson 2014.
*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment).
⬩Splenomegaly defined as vertical spleen length > 13 cm.
▪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

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, or 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, or 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.

APPENDIX 2. 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 to 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA, New York Heart Association.

APPENDIX 3. DOSE MODIFICATION TABLE FOR ZANUBRUTINIB WHEN CO-ADMINISTERED 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: CYP3A, cytochrome P450, family 3, subfamily A.

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/paritaprevir 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

Abbreviations: 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.

APPENDIX 5. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

APPENDIX 6. SCHEDULE OF ASSESSMENTS

Cycle		**C1**				**C2**		**C3**		**C4**	**C5**	**C6**	**C7 & Beyond**	**Suspected**			**SFU[a]**	**RFU[b]**	**LTFU**
														CR	**PD**				
Day		**1**	**8**	**15**	**21**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**				**30 days after EOT[c]**		**Every 3 months**
Window (Days)		**± 1**				**± 2**		**± 2**		**± 3**	**± 3**	**± 3**	**± 3**				**± 7**		**± 14**
Study Drug Administration																			
Zanubrutinib (continuous)		X	X	X	X	X	X	X	X	X	X	X	X						
Lenalidomide (Days 1-21 of each cycle)		X	X	X	X	X	X	X	X	X	X	X	X						
Procedure	**Screening Day -28 to -1**																		
Informed consent	X															**Continue Assessment Until Disease Progression**			
Biomarker tissue sample[d]	X									X					X				
Biomarker blood sample[e]	X									X			X		X				
Medical history & demographics	X																		
Concomitant medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Adverse events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Complete physical exam & weight (height Screening only)[h]	X	X				X		X		X	X	X	X				X		
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
ECHO[j]	X																		
Triplicate 12-Lead ECG[k]	X																		
Bone marrow aspiration/biopsy[l]	X													X					

Cycle		C1				C2		C3		C4	C5	C6	C7 & Beyond	Suspected			SFU[a]	RFU[b]	LTFU
														CR	PD				
Day		**1**	**8**	**15**	**21**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**				**30 days after EOT[c]**		**Every 3 months**
Window (Days)		**± 1**				**± 2**		**± 2**		**± 3**	**± 3**	**± 3**	**± 3**				**± 7**		**± 14**
Procedure	**Screening Day -28 to -1**																		
Confirm eligibility	X	X																	
Laboratory Assessments																			
Hematology[m]	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Serum chemistry[n]	X	X	X	X	X	X		X		X	X	X	X				X		
Coagulation (PT, INR, aPTT)[o]	X	X				X		X		X	X	X	X				X		
Thyroid function panel	X																X		
Hepatitis serologies[p]	X																		
Urinalysis[q]	X																		
Quantitative serum immunoglobulins (IgG, IgM, IgA)	X																		
Pregnancy test[r]	X	X	X	X	X	X		X		X	X	X	X				X		
PK blood sampling[s]		X			X														
Radiologic Tumor Assessment																			
CT neck, chest, abdomen, pelvis[t]	X									X			X	X	X[u]			X	
PET or PET/CT[t]	X									X			X	X	X[u]			X	
Other																			
Survival status																			X
Subsequent anticancer therapy																		X	X

Abbreviations: aPTT=activated partial thromboplastin time; C=cycle; CR=complete response; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment visit; INR=international normalized ratio; LTFU=Long-term Follow Up; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PO=oral; PT=prothrombin time; QTcF=Fridericia's corrected QT interval; RFU=Response Follow Up; SFU = Safety Follow Up

[a] An SFU visit will occur 30 days (±7) after the last dose of study drug (zanubrutinib, or lenalidomide, whichever is later), or before the start of a new anticancer treatment, whichever occurs first.

[b] Patients who discontinue for reasons other than PD continue to be followed for efficacy evaluations per protocol schedule until patient exhibits first progression, starts new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first.

[c] EOT is defined as end of treatment of zanubrutinib, or lenalidomide~~,~~ whichever is later.

[d] No less than 15 unstained slides with adequate tumor contents and quality must be sent to central laboratory for biomarker analysis, including determination of DLBCL subtype, EBV infection status, MYC/BCL2/BCL6 rearrangement or expression status, TCL1A expression, etc. If no archival samples are available, a fresh tumor biopsy collected at screening is required. For these patients, an optional biopsy for biomarker analysis after approximately 3 cycles of treatment is strongly recommended. Optional biopsy will be taken from patients who have confirmed disease progression during the study at accessible tumor sites to explore resistance mechanism.

[e] Blood samples will be collected at screening, scheduled response assessment visits, and at unscheduled visits when disease progression is to be confirmed to explore the association of blood-based biomarkers with response, resistance and prognosis. For more details, please refer to the Laboratory Manual.

[f] Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 4 weeks before Cycle 1 Day 1, and on study thereafter until 30 days after the last dose of zanubrutinib, or lenalidomide, whichever occurs later.

[g] After informed consent has been signed but before the administration of the study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of zanubrutinib, or lenalidomide, whichever occurs later. See Section 8 for details regarding the reporting of AEs.

[h] Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at Screening only).

[i] Vital signs (blood pressure, pulse, and temperature) will be assessed after the patient has rested in the sitting position for ≥3 minutes.

[j] An echocardiogram is to be performed at screening unless one has been performed within 30 days before the first dose.

[k] 12-lead ECG will be done in triplicate (≥1 minute apart). 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.

[l] A unilateral bone marrow aspiration and biopsy must be performed at screening if not performed within 60 days before the first dose for all patients, provided it is performed as part of their standard care and there has been no intervening therapy between the time of the biopsy and start of study drug. In those patients who had evidence of bone marrow disease at screening, upon achieving a possible CR (eg, physical exam or imagine indicating a possible CR), a bone marrow aspiration and biopsy should be obtained to confirm the CR.

[m] Hematology assessments (which include hemoglobin, hematocrit, platelets, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils and basophils) are required to be performed at screening, every visit during the treatment phase and Safety follow-up visit (if necessary as defined in Section 5.11).

[n] Serum chemistry assessments include sodium, potassium, chloride, urea or blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate or phosphorus, uric acid, magnesium, and bicarbonate (or CO_2 combining performance, CO_2CP). Chemistry assessments are required at screening, at Cycle 1, weekly on Day 1 of subsequent cycles and Safety follow-up visit (if necessary as defined in Section 5.11).

[o] Coagulation assessments (PT, INR, aPTT) are required at screening, Day 1 of subsequent cycles and Safety follow-up visit (if necessary defined in Section 5.11).

[p] Hepatitis serology (which includes hepatitis C antibody, HBsAg, HBsAb, and HBcAb) will be performed at screening. Patients who are HBcAb positive will undergo viral load measurement (HBV DNA by PCR) at screening and monthly during the study. Patients who are HCV antibody positive, will undergo viral load testing (HCV RNA by PCR) at screening and monthly during the study.

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

[r] Two negative pregnancy tests (at least one blood test) must be obtained before initiating therapy. The first test must be performed within 10-14 days before lenalidomide therapy and the second test within 24 hours before lenalidomide therapy. Urine pregnancy tests will be performed weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy tests must be continued every 4 weeks (cycle) for at least 90 days after the last dose of zanubrutinib and lenalidomide, whichever comes last. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

[s] Pharmacokinetic samples will be drawn according to the schedule in Table 2. Procedures for collection of samples are described in the Lab Manual. Additional PK samples may be taken if needed, to further evaluate zanubrutinib and lenalidomide exposure. The investigator will record the time of blood collection and the time of administration in the eCRF.

[t] Pretreatment tumor assessment should be performed within 28 days before the first dose. A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis, and any other disease sites and a PET or PET/CT scan are required for the pretreatment tumor assessment. During treatment, PET and contrast CT should be repeated every 12 weeks for the first 48 weeks, every 16 weeks for the next 48 weeks, and every 24 weeks thereafter until disease progression, use of alternative anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Disease assessment is performed on Cycle 4 Day 1 ± 3 days, Cycle 7 Day 1± 3 days, Cycle 10 Day 1 ± 3 days, Cycle 13 Day 1 ± 3 days, Cycle 17 Day 1± 3 days, Cycle 21 Day 1± 3 days, Cycle 25 Day 1± 3 days, Cycle 31± 3 days, etc. In the event that CT contrast is contraindicated, MRI may be performed as an alternative. Lesions in anatomical locations that are not well visualized by CT may be measured at baseline from MRI instead and should continue to be measured from MRI until disease progression.

[u] 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.

Signature Page

Approval	[redacted]