Clinical Study Protocol

Protocol Title:	**A Phase 2, Single arm, Multicenter, Open-label Study of Bruton's Tyrosine Kinase (BTK) inhibitor BGB-3111 in subjects with relapsed/refractory non-GCB type Diffuse Large B cell lymphoma**
Protocol Number:	**BGB-3111-207**
Date of Protocol:	**16 April 2018, Version 2.0**
Study Phase:	**2**
Sponsor:	**BeiGene (Beijing) Co., Ltd** **No. 30 Science Park Road,** **Zhong-Guan-Cun Life Science Park** **Changping district, Beijing 102206** **China**
Coordinating Investigator:	[redacted]
Sponsor Medical Monitor:	[redacted]

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SIGNATURES

PROTOCOL TITLE: A Phase 2, Single arm, Multicenter, Open-label Study of Bruton's Tyrosine Kinase (BTK) inhibitor BGB-3111 in subjects with relapsed/ refractory non-GCB type Diffuse Large B cell lymphoma

PROTOCOL NO: BGB-3111-207

[redacted] **Date**

Coordinating Investigator

[redacted] **Date**

Sponsor Medical Monitor

PROTOCOL AMENDMENT RATIONALE, VERSION 2.0

Protocol BGB-3111-207 (Version 2.0) is amended for the following reasons:

1. To remove Cohort 2, because adequate pharmacokinetics (PK)/pharmacodynamic (PD) data have been obtained from other BTK studies.
2. Sample size of Cohort 1 is reduced from 70 to 40 due to relevant adjustment in Beigene strategy.
3. Remove adverse events of special interest (AESI) to align with other protocols.
4. To clarify zanubrutinib dose reduction for non-hematologic toxicity
5. To replace independent Data Monitoring Committee (DMC) with Safety Monitoring Committee (SMC). It is because that at the early stage of clinical study, we focus more on safety than on efficacy, so the efficacy data will not be evaluated by committee in this Phase 2 study.
6. To revise and clarify some eligible criteria.

In addition, some contents (including administrative information, language, and format) are modified to improve the clarity and consistency throughout the document. Changes were made to the synopsis to match changes made in the protocol body.

Substantial Changes:

- Replaced the compound name of BGB-3111 with its international non-proprietary name, zanubrutinib, throughout this document (except for reference).
- Original Section 6.1.1 was moved in Section 1.7 (Zanubrutinib Pharmacokinetics and Pharmacodynamics), the wording was updated for clarification.
- Section 2.3 (Exploratory Objective): [redacted]
- Section 3.2 (Secondary Endpoints): removed the safety endpoints related to AESI.
- Section 3.3 and 10.1.3 (Exploratory Endpoints): [redacted]
- Section 4.1: revised the sample size as 40 subjects, clarify the treatment phase and the duration of the follow-up phase, and revised wording for clarification.
- Figure 1: revised as “Safety Follow-up visit (**30 ± 7** days after last dose)”.
- Removed Cohort 2 in Figure 1 and remove the original Figure 2.

- Section 5.1 (Inclusion Criteria)
    - #5: updated the period of tumor tissue sample collection to **within 2 years of study entry** and removed the wording related to Cohort 2.
    - #9: revised neutrophils assessment as within 7 days **of first dose of study drug**
    - #10: revised platelets assessment as within 7 days **of first dose of study drug**
    - #14: replaced "Hemoglobin ≥ 8g/dL" with "**Independent of erythropoietin (EPO) support or transfusion within 7 days of first dose of study drug"**
- Section 5.2 (Exclusion Criteria): in #11, replaced prophylactic entacavir with **anti-HBV medication** and clarified that patients who receive anti-HBV medication will have HBV DNA test every 3 cycles**;** in #14, removed Chinese herbal medications.
- Section 6.1 (Study Treatment): removed wording related to Cohort 2 and revised the wording for clarification.
- Section 6.2.1 (Packaging and Labeling): removed bottle number.
- Section 6.4 (Dosage and Administration): revised to clarify that patients will take zanubrutinib with water at approximately the same time every day, **with a minimum of 8 hours between consecutive doses;** and removed wording related to Cohort 2.
- Section 6.5.2 (Dose Reductions for Non-Hematologic Toxicity): updated wording for clarification.
- Section 7.1 (Study Flow and Visit Schedule, Table 2), added time windows for Safety Follow-up Visit (30 **± 7 days**) and Survival Follow-up (**every 3 months ± 7 days**); in #10 e, clarified that patients who receive anti-HBV medication will have HBV DNA test every 3 cycles, removed the wording related to Cohort 2 and PK/PD, added a line for urine or serum pregnancy test, and revised the footnotes to be consistent with other sections.
- Section 7.1, removed the original Table 3 and Table 4 because they are PK/PD related.
- Section 7.4.5.4 (Coagulation), add activated partial thromboplastin time (screening only) for consistency.
- Section 7.4.6 (Electrocardiogram), removed the wording related to PK/PD.
- Removed the original sections of Pharmacokinetics (original in Section 7.5), Pharmacodynamic Biomarkers (original in Section 7.6.2), and Pharmacogenetics (original in Section 7.6.3).

- Section 9.1.1.1 (Period and Method of Detecting AEs and SAEs), revised wording for clarification.
- Remove original Section 9.5 (Adverse Events of Special Interest)
- Section 9.5 (Safety Monitoring Committee): replaced independent DMC with **SMC**, clarified that efficacy data will not be evaluated, and updated that early safety review will occur about 3 months after enrollment of the 25th subject.
- Section 10.1.2 (Secondary Endpoints): removed the safety endpoints related to AESI and PK.
- Section 10.2.1 (Analysis Populations): removed the wording related to PK analysis.
- Section 10.2.3 (Demographics and Other Baseline Characteristics): remove race, geographic region, and blastoid histology from this section.
- Section 10.2.5.1 (Primary Efficacy Analysis); removed the hypothesis testing from this study.
- Section 10.2.5.3 (Exploratory Efficacy Analysis): [redacted].
- Removed original Section 10.2.6 (Pharmacokinetic Analysis) and original Section 10.2.7 (Biomarker/Pharmacodynamic Data, If Applicable)
- Section 10.3.1 (Extent of Exposure): removed “dose delay” and clarified the wording.
- Section 10.3.2 (Adverse Events): removed the wording related to AESI.
- Section 10.4 (Sample Size Consideration): updated the sample size as 40.
- Section 10.6 (Other Statistical Issues): revised as “Not applicable”.
- Section 11.4 (Study and Study Center Closure): removed the wording related to PK samples.

SYNOPSIS

Name of Sponsor/Company:	**BeiGene (Beijing) Co., Ltd**
Name of Finished Product:	**Zanubrutinib (BGB-3111)**
Name of Active Ingredient:	**Zanubrutinib**
Title of Study:	A Phase 2, Single arm, Multicenter, Open-label Study of Bruton's Tyrosine Kinase (BTK) inhibitor BGB-3111 in subjects with relapsed/refractory non-GCB type Diffuse Large B cell lymphoma
Protocol No:	BGB-3111-207
Study duration: Screening (up to 28 days); daily treatment until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination from sponsor; treatment (up to 2 years), safety follow-up (30 days); survival follow-up until data cutoff for final analysis.	Phase: 2

Objectives:

Primary:

To evaluate the efficacy of zanubrutinib at a dose of 160 mg orally (PO) twice daily (BID), in subjects with relapsed or refractory non-Germinal Center B cell type Diffuse Large B cell Lymphoma (non-GCB DLBCL) as assessed by the objective response rate according to the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria (Cheson et al 2014).

Secondary:

To evaluate the efficacy of zanubrutinib as measured by progression free survival (PFS).

To evaluate the efficacy of zanubrutinib as measured by duration of response (DOR).

To evaluate the efficacy of zanubrutinib as measured by time to response (TTR).

To evaluate the safety and tolerability of zanubrutinib at a dose of 160 mg PO BID in subjects with relapsed or refractory non-GCB type DLBCL.

Exploratory:

[redacted]

Methodology:

This is a single-arm, multicenter, open-label Phase 2 study to evaluate efficacy, safety, tolerability of zanubrutinib in subjects with relapsed/refractory non-GCB type Diffuse Large B Cell Lymphoma.

The study will enroll approximately 40 subjects treated with zanubrutinib 160mg BID. All subjects in the study will be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. At the time of final analysis, subjects who remain on treatment will be considered for participation in the extension study when eligible. A treatment cycle consists of 28 days.

Planned number of subjects:	Approximately 40 subjects will be enrolled.

Study Population	Inclusion criteria: 1. Histologically confirmed non-germinal center diffuse large B cell lymphoma (DLBCL), by immunohistochemistry using the Hans algorithm, a. CD10- and BCL6-, b. CD10-, BCL6+, but MUM1+ 2. Men and women ≥ 18 years of age. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. 4. Measurable disease is defined as at least 1 lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions. 5. All subjects must provide fresh tumor biopsy or recent tumor tissue samples (within 2 years of study entry [informed consent form signed]). 6. Received at least one prior therapy for DLBCL that includes anthracycline based chemotherapy. 7. Patient not eligible for or refuses intensive chemotherapy and hematopoietic stem cell transplant. 8. Documented failure to achieve at least partial response (PR) with, or documented disease progression after response to, the most recent treatment regimen. 9. Neutrophils ≥ 1 x 10^9/L independent of growth factor support within 7 days of first dose of study drug. 10. Platelets ≥ 75 x 10^9/L, independent of growth factor support or transfusion within 7 days of first dose of study drug. 11. Creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]). 12. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN). 13. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome, then up to 5xULN allowed). 14. Independent of erythropoietin (EPO) support or transfusion within 7 days of first dose of study drug. 15. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN. 16. Subjects may be enrolled who relapse after autologous stem cell transplant, at least 6 months after transplant, subjects should have no active infections (ie, fungal or viral). 17. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control can be defined as abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for up to 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization– vasectomy, or utilize a barrier method where the female partner utilizes the effective forms of birth control noted above. 18. Life expectancy of > 3 months. 19. Able to provide written informed consent and can understand and comply with the requirements of the study.

Exclusion criteria:

1. Current or history of central nervous system (CNS) lymphoma.
2. Prior exposure to a BTK inhibitor.
3. Prior corticosteroids (at dosages equivalent to prednisone > 20 mg/day) given with anti-neoplastic intent within 7 days, prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, or antibody based therapies or Chinese anti-cancer herbal therapies within 4 weeks of the start of study drug.
4. Major surgery within 4 weeks of screening.
5. Toxicity of ≥ Grade 2 from prior anti-cancer therapy (except for alopecia, absolute neutrophil count (ANC) and platelets. For ANC and platelets, please follow inclusion criteria #9 [neutrophils] and #10 [platelets]).
6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
7. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification, or history of myocardial infarction within 6 months of screening. Left Ventricular Ejection Fraction (LVEF) is lower than 50% measured by echocardiography (ECHO) (AHA,2016).
8. QTcF (Fredericia's correction) > 450 msecs or other significant electrocardiogram (ECG) abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block.
9. 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.
10. Uncontrolled systemic infection or infection requiring parenteral anti-microbial therapy.
11. Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR]).

	Inclusion		**Exclusion**	
HIV	Antibody (-)		Antibody (+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA<1000 IU/mL, After enrollment, check HBV DNA monthly or every 3 cycles for patients receiving anti-HBV medication to prevent HBV reactivation	HBsAg(-) HBcAb(+)	HBV DNA ≥1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA<1(log_{10}IU/mL) and monthly monitoring, or treatment with anti-HCV medication.	Antibody(+)	HCV RNA ≥1(log_{10}IU/mL)

HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

HBV evaluation includes HBsAg, HBcAb, HBsAb. If subject is HBsAg- but HBcAb+ (without considering HBsAb status), will evaluate HBV DNA using PCR, the acceptable upper limit is 1000IU/ml, however, because different assays are used in different hospitals, the acceptable upper limit will be that of the upper limit at the hospital where the test is conducted. HCV evaluation involves the HCV Ab, if positive, to evaluate HCV RNA as above.

	12. Pregnant or lactating women. 13. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk. 14. On medications which are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or CYP3A inducers (Appendix 4).
Test product, dose and mode of administration:	Zanubrutinib 160 mg (two - 80 mg white opaque capsules) PO BID
Reference therapy, dose, and mode of administration:	Not applicable

Study Treatment:

Zanubrutinib 160 mg will be administered as two 80-mg capsules by mouth twice a day with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Treatment with zanubrutinib may be continued until disease progression, unacceptable toxicity, or withdrawal of consent. At the time of final analysis, subjects who remain on treatment will be considered for participation in the extension study. A treatment cycle consists of 28 days.

The guidelines set forth in Table 1 should be followed for dose interruption or modification of zanubrutinib for hematologic, non-hematologic toxicities.

Table 1: Zanubrutinib Dose Reduction Steps

Dose Level	Zanubrutinib Dose
Starting Dose	160 mg BID
Dose Level -1	80 mg BID
Dose Level -2	80 mg QD

BID=twice daily; QD=once a daily

Study drug (zanubrutinib) may be held for a maximum of 28 consecutive days. If, in the Investigator's opinion, it is in the subject's best interest to restart study drug after more than 28 days, then written approval to be issued by the sponsor medical monitor after request by investigator.

Dose Modifications for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting >7days, however, earlier interruption acceptable if medically indicated)
- Grade 4 thrombocytopenia (lasting >7days, however, earlier interruption acceptable if medically indicated)
- ≥Grade 3 febrile neutropenia
- ≥Grade 3 thrombocytopenia associated with bleeding

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the platelet count to $\geq 75\times10^9$/L, neutrophil recovery to $\geq 1\times10^9$/L. If the same event reoccurs, subjects will restart at one dose level lower upon recovery. A maximum of 2 dose reductions will be allowed. Subjects

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

Asymptomatic treatment-related lymphocytosis should not be considered an AE (Cheson et al 2012). Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Dose Reductions for Non-Hematologic Toxicity

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

Concomitant Therapy and Clinical Practice:

Prohibited Concomitant Therapy

During study treatment, subjects are prohibited from receiving any anticancer therapy, including but not restricted to chemotherapy, immunotherapy, corticosteroids (at dosages equivalent to >20mg/day of prednisone), experimental therapy, radiotherapy, and Chinese herbal medications are prohibited. Corticosteroid courses (at dosages equivalent to prednisone >20mg/day) of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition. Bisphosphonates that have been in steady use for over 3 months are permitted.

Drugs known to prolong the QT/QTc interval are prohibited

In accordance with the Food and Drug Administration (FDA) Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Drugs known to prolong QT interval should be avoided, it they have to be prescribed, it has to be agreed to by the sponsor's medical monitor. A link to a list of drugs with QTc prolongation potential is provided through the https://crediblemeds.org/, and is also provided in Appendix 2.

Concomitant Use of CYP3A Inhibiting Drugs

The primary metabolic pathway for zanubrutinib involves the cytochrome P450, family 3, subfamily A (CYP3A) isoform. Strong CYP3A4 inhibitors or strong inducers must be avoided. If no alternative treatment is available, zanubrutinib should be stopped for the duration of CYP3A4 inhibitor or inducer usage; subjects should be closely monitored for potential toxicities with temporary interruption of zanubrutinib.If the subject requires treatment with moderate CYP3A4 inhibitors or inducers, the medical monitor should be consulted for potential toxicity (see Appendix 4).

Criteria for Evaluation:

Response will be evaluated based on investigator review using the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria (Appendix 3). Patient will receive a positron emission tomography (PET) and contrast computed tomography (CT) at screening, after 12 and 24 weeks of therapy, and at suspected complete remission. Contrast CT alone will be performed at weeks 36, 48, and thereafter, once every 16 weeks. Response will be assessed on the basis of radiological evaluations. Bone marrow biopsy will be required for confirmation of complete response ([CR] at first occurrence of radiological and clinical evidence of CR) in subjects with bone marrow tumor involvement prior to study drug. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.

The safety of this study will be monitored by a Safety Monitoring Committee (SMC), its organization and detailed execution will be written in the SMC charter. The SMC will evaluate safety data, and advise accordingly. Subjects will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI CTCAE v. 4.03]) and serious AEs (SAEs). Subjects who, at time of progression, have an ongoing AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the subject is lost to follow-up, or the subject starts a different anti-tumor therapy.

A significant safety event (SSE) is defined as any of the following:

- General toxicity (NCI CTCAE V.4.03): Grade 3 and Grade 4 AEs, SAEs.
- Any adverse event that requires dose interruption, reduction or discontinuation of the study drug.
- A subject's death.

In the case of major toxicity concerns, the SMC can recommend to modify the trial conduct.

Endpoints:

Primary Endpoint:

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or complete response (CR) by the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson et al 2014) (Appendix 3) at any time on study drug.

Secondary Endpoints

Efficacy:

- Progression free survival (PFS): defined as time from first dose of zanubrutinib until first documentation of progression (by IWG on NHL criteria) or death, whichever comes first
- Duration of response (DOR) is defined as the time from the date that the response criteria are first met to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.
- Time to response (TTR) is defined as the time from first dose of zanubrutinib to documentation of a response.

Safety:

- To evaluate the safety and tolerability of zanubrutinib, as defined by:
  - The incidence and severity of treatment-emergent adverse events (TEAEs), SAEs and treatment-related AEs according to NCI CTCAE v4.03
  - The incidence, severity, timing, and causation of adverse events leading to study drug discontinuation.

Exploratory Endpoints:

- [redacted]

Statistical Methods:

Populations:

The Safety Population includes all subjects who received any dose of zanubrutinib. This will be the population for the efficacy and safety analyses.

The Per-Protocol Population (PP) includes subjects who received any dose zanubrutinib and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analysis

Primary Efficacy Analysis:

The ORR in this study is estimated as 35%, which is deemed a clinical meaningful improvement.

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate. No hypothesis testing will be done.

Best overall response (BOR) is defined as the best response recorded from the start of zanubrutinib until data cut or start of new anti-neoplastic treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, stable disease [SD], and PD) will be presented.

The primary efficacy analysis will be conducted no later than 12 months after the first dose of the last subject, and will be based on the safety population.

Secondary Efficacy Analysis:

Kaplan-Meier (KM) method will be used to estimate progression event-free curves and corresponding quartiles (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 subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula.

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

Time to event variables (DOR and TTR) will be similarly analyzed using the KM method as described above. The KM estimates of DOR and TTR will be plotted over time.

Sensitivity analysis will be performed for primary and secondary endpoints in the PP population.

Exploratory Efficacy Analysis:

[redacted]

Safety Analysis:

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded according to the NCI CTCAE v.4.03. All treatment emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or was worsening in severity from baseline

(pretreatment). Serious adverse events, deaths, TEAEs with Grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Multiple occurrences of the same event will be counted once at the maximum severity within a system organ class (SOC) and preferred term (PT).

Clinical laboratory data with values outside of the normal ranges will be identified. Select laboratory data will be summarized by grade. Vital signs will also be summarized by visit.

Sample Size:

Approximately 40 subjects will be enrolled. The precision of the estimated ORR is used in the sample size calculation. Assuming an ORR of 35%, the 95% exact confidence interval will be 20.6% to 51.7%.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B-cell
ADCC	antigen-dependent cell-mediated cytotoxicity
AEs	adverse events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AV	atrioventricular
BCR	B-cell receptor
BID	twice a day
BOR	best overall response
BP	blood pressure
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CERT	Center for Education and Research on Therapeutics
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP	cytochrome
CYP3A	cytochrome P450, family 3, subfamily A
DBP	diastolic blood pressure
DDI	drug-drug interaction
DLBCL	diffuse large B cell lymphoma
DOR	duration of response
EC	expansion cohort

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
eGRF	estimated glomerular filtration rate
EGFR	epithelial growth factor receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FGR	Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
GCB	Germinal center B-cell type
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HDPE	high density polyethylene
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
ITK	interleukin-2-inducible T cell kinase
JAK3	Janus kinase 3
KM	Kaplan-Meier
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LVEF	left ventricular ejection fraction

MCL	mantle cell lymphoma
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NTI	narrow therapeutic index
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PLCβ2	phospholipase C-beta-2
PO	per os (orally)
PP	per-protocol population
PR	partial response
PT	preferred term or prothrombin time
RBCs	red blood cells
R-CHOP	rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
SAEs	serious adverse events
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SMC	Safety Monitoring Committee
SOC	system organ class
SOPs	standard operating procedures
SSE	significant safety event
TEAEs	treatment emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TLS	tumor lysis syndrome
TTR	time to response

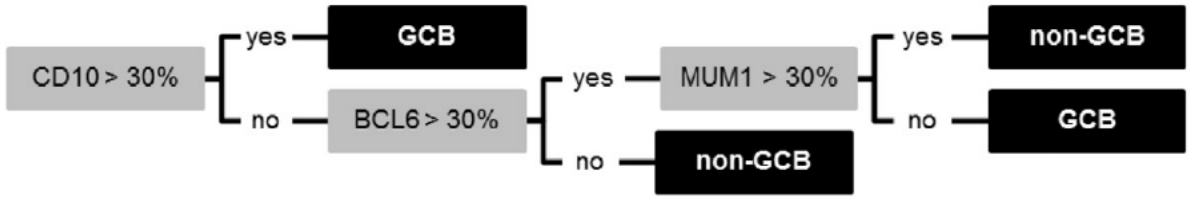
ULN	upper limit of normal
WBCs	white blood cells
WHO-DD	World Health Organization Drug Dictionary
zanubrutinib	BGB-3111

1 INTRODUCTION

1.1 Current Status of Diffuse Large B cell Lymphoma Care

In 2012, there were 386,000 new non-Hodgkin's lymphoma (NHL) patients diagnosed worldwide, at an incidence rate of 5.1/100,000 population, in the same year, there were 200,000 deaths from the illness (GLOBOCAN 2012). In 2016, 72,580 new NHL patients will be diagnosed in the US, with 20,150 dying from the disease, 5 years survival has already risen to 70.7%. Diffuse large B cell lymphoma (DLBCL) made up 37% of NHL patients (Morton et al 2006). In China, the incidence of non-Hodgkin's lymphoma is 5 /100,000 population, contributing 65,000 new cases a year; DLBCL makes up 40% of the new cases. The median age for diagnosis is 60-70 years, with a slight preponderance of males.

DLBCL is the most common type of NHL, morphologically, it consists of large cells with nuclei larger than that of macrophages, the lymphoma cells express the B cell antigens CD19+, CD20+, CD22+, CD79a+, and often are CD45+, but have to be CD3-, subgroups can be CD63+ (primary cutaneous B cell lymphoma, leg type), CD5+ (CD5 + DLBCL), CD10+ (GCB subtype), CD138+ (plasmablastic differentiation), CD30+ (which could be either CD30 + DLBCL or PMBL or Hodgkin's lymphoma), IRF/MUM1+ (ABC type), BCL2 and BCL6 can be positive or negative in the GCB and non-GCB subtypes. There are many subtypes of DLBCL, defined by the organ in which DLBCL is located at diagnosis, age of the patient, associated infectious agent, and also by overlap with Burkitt's lymphoma or Hodgkin's disease (Xie et al 2015). In 2000, gene expression profiling (GEP) separated the morphologically similar DLBCLs into different types, the most common being the germinal center type (GCB) with genes akin to germinal center B cells, and the non-GCB or activated B cell (ABC) type, with genetic pathways in alignment with activated peripheral blood B cells. The GCB type enjoys a significantly superior 12 years survival of 60-75%, in contrast to 25-40% for the non-GCB type after first line treatment with standard immuno-chemotherapy of rituximab, cyclophosphamide, doxorubicin, prednisolone (R-CHOP) (Alizadeh et al 2000). GEP is costly and difficult to execute clinically. In 2004, the Hans algorithm based on immunohistochemical markers was developed for simplified subtype differentiation (Hans et al, 2004). Both GEP and the Hans algorithm were separately demonstrated to correlate with the International Prognostic Index (IPI), and immunohistochemistry (IHC) is still in the mainstream for diagnosis in the present day (Agarwa et al, 2016). Many algorithms have been developed for subtyping of DLBCL, however, for this phase II trial, the Hans algorithm will be used (Gifford et al 2016).



About 10-15% of DLBCLs are so called double and triple hit lymphomas (de Jonge et al 2016), there is a fundamental t(8;14) with c-myc over-expression, and concurrent abnormalities / over-expression of bcl-2, and/or bcl-6; this poor prognosis group has a significantly inferior survival of only 35% at 2years after R-CHOP (Barrans et al, 2010), over and above that would be expected from the IPI score. CARD11 mutations detected in 11% of DLBCL impacts the CBM complex of BCL10, CARD11, and MALT1, A30(inhibitor of CBM complex) mutations occur in 30%, 18% DLBCL tumors have CD79B ITAM region mutations, all can impact B cell receptor pathway drug efficacy. In a clinical study of 187 Korean DLBCL patients, CD79B mutation was found in 16 cases (8.5%), of whom 11cases also carried the MYD88 mutation; and MYD88 with L265P mutation was detected in 19.3% of cases, but neither mutation seemed to have an impact on disease outcome. However, Toll like receptor antagonists have demonstrated efficacy in vitro, and have been advanced into clinical trials to rectify the purported resistance to BTK inhibitors from such mutations.

DLBCL patients are staged according to the Ann Arbor classification, just under a third of patients have stage I or II disease (ie, disease confined to 1 side of the diaphragm) at diagnosis, a third present with bulky disease (> 7.5 cm), about 40% have extranodal involvement, 20% have marrow involvement, although neither staging nor B symptoms (weight loss, fever, night sweats) have been definitively linked to prognosis. An international prognostic score (IPI) was developed in 1993 in the pre-rituximab era, and is still applicable in the present day, although it has been simplified and modified in the post rituximab era. One point each is allocated for age>60yrs, stage III/IV disease, increased lactate dehydrogenase (LDH), ECOG performance status >2, >2 extranodal site involvement, patients are thus stratified into 3 risk groups of very good (0 points), good (1 or 2 points), and poor (3-5 points), with respective 5 year disease free and overall survival rates of 94%/94%, 80%/80%, and 53%/55% (Zelenetz et al 2016). IPI scores have also been modified for geriatric patients, and patients with central nervous system involvement which will not be needed for the present clinical trial.

Since 2004, R-CHOP has become first line therapy for DLBCL patients, with 3yr overall survival (OS) rates ranging from 59% to 91%, depending on the IPI scores. Unfortunately, 30-40% of patients will eventually relapse and require salvage treatment. The patients are then practically divided into a group amenable to intensive treatment, followed by bone marrow transplantation (Camicia et al 2015), and a left over group not amenable to such treatment for varying reasons, most

commonly, age over 65yrs, and these patients are to receive more moderate therapy. Regimens for relapsed and refractory disease can be more intense and toxic, and has to be followed by bone marrow rescue, regimens such as DHAP (dexamethasone, cisplatin, cytarabine), ESHAP (VP-16, cytarabine, cisplatin, methylprednisolone), GEMOX (gemcitabine and oxaliplatin), ICE (ifosfamide, carboplatin, etoposide), all with or without rituximab, these regimens often incur significant morbidity in themselves. For those who are not candidates for intensive treatment, regimens recommended include bendamustine, brentuximab vedotin (if CD30+), GEMOX, lenalidomide, often with rituximab, there is no definitive recommended regimen that has been show to superior to all others.

When patients relapse, it can be as a result of original tumor heterogeneity, with positive selection for subclones carrying intrinsic genetic or epigenetic resistance mechanisms, treatment induced, or through interaction of the tumor with its micro- environment. BTK inhibitors can play a significant role in the control of the non-GCB type DLBCLs, which demonstrated activation of the B-cell receptor (BCR) pathway and downstream NKκB activation. BTK inhibitors have demonstrated efficacy in the proof of concept study in non-GCB DLBCL patients, with a good toxicity profile, and quality of life. Zanubrutinib is a best in class BTI inhibitor, and will hopefully open up a new era of B-cell malignancy control.

1.2 Zanubrutinib

Zanubrutinib (also known as BGB-3111) is a novel second generation small molecule oral BTK inhibitor, which forms an irreversible covalent bond at Cys481 within the adenosine triphosphate (ATP) binding pocket of the BTK protein. Zanubrutinib is highly potent against BTK; however, as opposed to ibrutinib, zanubrutinib has significantly less epithelial growth factor receptor (EGFR)/Janus kinase 3 (JAK3)/ tyrosine kinase expressed in hepatocellular carcinoma (TEC)/interleukin-2-inducible T cell kinase (ITK) inhibitory activity, thus potentially reducing the side effects seen with ibrutinib and allowing increased exposure with potentially improved efficacy.

1.3 Non-Clinical Data

Zanubrutinib inhibits BTK with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomolar (nM) in biochemical assays. Cellular assays confirmed that zanubrutinib inhibited B-cell receptor (BCR) aggregation-triggered BTK autophosphorylation, and blocked downstream phospholipase C-beta-2 (PLCβ2) signaling in mantle cell lymphoma (MCL) cell lines. Zanubrutinib potently and selectively inhibited cellular growth of several MCL cell lines (REC-1, Mino and JeKo-1) and activated B-cell (ABC) type of diffuse large B-cell lymphoma (DLBCL) cell line TMD8, with IC_{50}s from 0.36 nM to 20 nM, while inactive in many other hematologic cancer cell lines. In vivo studies showed that zanubrutinib induced dose-dependent anti-tumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib was more

selective than ibrutinib for inhibition of kinase activity of BTK vs. EGFR, Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), fyn-related kinase (FRK), human epidermal growth factor receptor (HER)2, HER4, ITK, JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antigen-dependent cell-mediated cytotoxicity (ADCC). Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced ADCC, consistent with zanubrutinib being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays, thus preventing the potential for antagonism with rituxan that has been seen pre-clinically with other BTK inhibitors.

1.4 Zanubrutinib global Phase 1 Clinical Experience

The first-in-human study with zanubrutinib, which was designed to look at safety and pharmacokinetics in subjects with B-cell lymphoid malignancies, started in Australia in August 2014. As of 28 February 2016, a total of 95 subjects have been enrolled; 25 subjects in dose escalation and 70 subjects into one of the four dose expansion cohorts (ECs); dosing in EC included 57 subjects receiving 160 mg twice daily and 13 subjects receiving 320 mg daily. A total of 57 subjects are considered fully evaluable for efficacy and safety, defined as having been enrolled for at least 12 weeks prior to the latest data cut-off date (21 January 2016).

Median follow-up is 212 days (range 10-492). The maximum tolerated dose (MTD) was not reached. Zanubrutinib was well tolerated; in 82% of subjects no drug-related AEs of ≥ Grade 2 were reported within the first 12 weeks of therapy. As of the cut-off date, only 3 subjects discontinued zanubrutinib due to adverse events (AEs), including 2 subjects due to complications related to refractory underlying malignancy and 1 patient due to worsening of bronchiectasis. Six subjects (11%) experienced a Grade >3 toxicity believed by the investigator to be related to zanubrutinib, including 5 cases of transient neutropenia and 1 case of Grade 3 hypertension. Grade 1 or 2 toxicities reported, regardless of attribution, with an incidence of greater than 15%, include petechiae/ contusion/ bruising (39%), diarrhea (28%), cough (28%), upper respiratory infection (26%), fatigue (23%), rash (18%), and constipation (18%).

1.5 Zanubrutinib in Relapsed or Refractory DLBCL global clinical trial

Up until June 10th, 2016, in subjects that are fully evaluable for safety and efficacy, 15 cases were diagnosed as DLBCL, 7 (47%) patients have attained response to treatment.

1.6 Zanubrutinib Phase I clinical trial in China

The IND package for zanubrutinib was approved by the CFDA in February of 2016. Phase I clinical trial (BGB-3111-1002） was initiated in July 2016, 2 dose schedules of 320 mg QD or160 mg BID

were tested, with evaluation of pharmacokinetics, safety, and tolerability in Chinese B cell lymphoma patients. By the end of October, 2 groups of 21 patients, 11 on 160 mg BID, and the rest on 320mg QD, had all passed the one month DLT evaluation period, including 16 males and 5 females, ranging in age between 35-72 years, including 9 chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma, 6 cases follicular lymphoma, 2 cases each of MCL, marginal zone and Waldenstrom's macroglobulinemia. Up until October 27th, 2016, zanubrutinib related adverse events $\geq$ Grade 3 included one Grade3 and 2 Grade 4 neutropenia，the remaining were all Grade 2 AEs, including 1 neutropenia, 1 anemia, 2 asymptomatic QTcF prolongation and 1 upper respiratory tract infection. So far, 5 patients have had their first 12-week evaluation, all have attained partial response, 3 CLL, 1 Waldenstom macogloulinemia, and 1 follicular lymphoma. Zanubrutinib induced physiological lymphocytosis, which was correlated with concurrent decrease in lymphadenopathy.

1.7 Zanubrutinib Pharmacokinetics and Pharmacodynamics

The pharmacokinetic data of zanubrutinib has been based on 76 B cell lymphoma patients, 1113 serum samples. These patients received doses between 40 to 320mg daily, when given as a single dose, at steady state, the maximum observed plasma concentration (C_{max}) and area under the plasma concentration time curve $(AUC)_{0\text{-}24h}$ increase was linear. Absorption of zanubrutinib is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 5 hours at 320 mg daily. Clearance and distribution is 136L/h and 300L respectively.

At 80 mg/d of zanubrutinib, drug exposure (C_{max} and $AUC_{0\text{-}24h}$）approximated ibrutinib dosed at 560mg/day。The free drug ratio between zanubrutinib and ibrutinib were 5.8% and 2% respectively，therefore, theoretically zanubrutinib dosed at 40mg/day would attain equivalent free drug exposure (C_{max} and $AUC_{0\text{-}24h}$） to Ibrutinib given at 560mg/day. In the 320 mg QD and 160 mg BID groups，the zanubrutinib steady state free drug exposure (C_{max} and $AUC_{0\text{-}24h}$）are 646 ng/mL and 2,704 ng/mL*h, or 282 ng/mL and 3,006 ng/mL*h respectively. In zanubrutinib global phase I clinical trial, plasma exposure on18 Korean patients dosed at 160 mg BID were similar to Caucasians.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all subjects in the study, while occupancy in lymph node tissue was assessed only at 160 mg twice daily and 320 mg daily. At the 160 mg BID dose, full BTK occupancy was observed at trough exposure periods, 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 indications 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 daily; both schedules show a high level of activity without compromise of the tolerability profile as compared to lower doses of

zanubrutinib. Therefore, 160 mg PO BID is selected as the recommended Phase 2 dose based on sustained target occupancy, high rates of objective response in multiple histologies, and a favorable safety and tolerability profile.

Cytochrome P450, family 3, subfamily A (CYP3A) was the major CYP isoform responsible for zanubrutinib metabolism. Zanubrutinib is a moderate inhibitor for CYP2C8 (IC_{50} = 4.03 μM), CYP2C9 (IC_{50} = 5.69 μM) and CYP2C19 (IC_{50} = 7.80 μM) while the IC_{50}s for other CYP isozymes are all larger than 10 μM. Zanubrutinib is not a time-dependent CYP inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Drug-drug interactions between zanubrutinib and CYP2C8, CYP2C9, and CYP2C19 substrates would be dependent on final plasma levels obtained in humans at therapeutic doses. Zanubrutinib is not an inducer of human CYP1A2, CYP2B6 but have weak CYP3A induction potential at concentration equal or higher than 3 μM in primary human hepatocytes. For this reason, caution must be used when using strong CYP3A activators as in Appendix 4.

In the food effect study, a high fat meal did not impact the plasma exposure of zanubrutinib AUC and C_{max} are increased by 37% and 56% respectively after a low-fat meal. Since this increase is still within the variability of zanubrutinib exposure (approximately 50% CV), and given zanubrutinib has a larger therapeutic window, effect of food on zanubrutinib bioavailability is not considered to be clinically relevant. Therefore, there will be no food restriction in this study, patients can choose to be fasting or take zanubrutinib after a meal, and should try to take the capsules under similar conditions each day.

1.8 Zanubrutinib in non-GCB Diffuse Large B Cell Lymphoma

Bruton's tyrosine kinase (BTK), a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, is a critical component of the B-cell receptor (BCR) signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib, the first-in-class Food and Drug Administration (FDA)-approved BTK inhibitor, has demonstrated promising anti-tumor activity in MCL, CLL, and Waldenstom macogloulinemia.

Zanubrutinib is a potent, specific and irreversible BTK inhibitor. The data generated in preclinical studies using biochemical, cell based and animal studies suggest that zanubrutinib could offer significant patient benefit in inhibiting tumor growth in non-GCB DLBCL, and as zanubrutinib was shown to be more selective than ibrutinib for inhibition of BTK, may have a favorable side effect profile, allowing for higher and more prolonged exposure to drug, allowing for more sustained BTK inhibition, potentially enhancing clinical efficacy.

For these reasons, we believe that a single-arm Phase 2 open-label study of the Bruton's tyrosine kinase inhibitor zanubrutinib, in subjects with relapsed or refractory non-GCB DLBCL is warranted, especially with the aim to find molecular markers associated with efficacy endpoints.

The lack of treatment-related SAEs and preliminary efficacy results from the Phase 1 study supports further investigation of 160 mg PO BID in subsequent Phase 2 and Phase 3 studies to confirm the benefit/risk profiles of zanubrutinib in B-cell malignancies. Refer to the Investigator's Brochure (IB) for more detailed information on the background of zanubrutinib.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of zanubrutinib at a dose of 160 mg orally (PO) twice daily (BID), in subjects with relapsed or refractory non-Germinal Center B cell type Diffuse Large B cell Lymphoma (non-GCB DLBCL) as assessed by the objective response rate according to the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria (Cheson et al 2014).

2.2 Secondary Objective

To evaluate the efficacy of zanubrutinib as measured by progression free survival (PFS).

To evaluate the efficacy of zanubrutinib as measured by duration of response (DOR).

To evaluate the efficacy of zanubrutinib as measured by time to response (TTR).

To evaluate the safety and tolerability of zanubrutinib at a dose of 160 mg PO BID in subjects with relapsed or refractory non-GCB type DLBCL.

2.3 Exploratory Objective

[redacted]

[redacted].

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or complete response (CR) by the 2014 modification of the

International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson et al 2014) (Appendix 3) at any time on study drug.

3.2 Secondary Endpoints

Efficacy:

- Progression free survival (PFS): defined as time from first dose of zanubrutinib until first documentation of progression (by IWG on NHL criteria) or death, whichever comes first.
- Duration of response (DOR) is defined as the time from the date that the response criteria are first met to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.
- Time to response (TTR) is defined as the time from first dose of zanubrutinib to documentation of a response.

Safety:

- To evaluate the safety and tolerability of zanubrutinib, as defined by:
    - The incidence and severity of treatment-emergent adverse events (TEAEs), SAEs and treatment-related AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE v4.03).
    - The incidence, severity, timing, and causation of adverse events leading to study drug discontinuation.

3.3 Exploratory Endpoints

[redacted]

4 STUDY DESIGN

4.1 Summary of Study Design

This is a single-arm, open-label, multi-center Phase 2 study in subjects with histologically documented non –GCB DLBCL who have relapsed after ≥ 1 prior treatment regimen including rituximab(s), patients also have to be ineligible for intensive chemotherapy and bone marrow transplantation. The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase of up to 2 years, and a follow-up phase (30 days), at the end of which if the patient is still benefiting from therapy, will be allowed to join the long term extension study.

Up to approximately 40 subjects will be enrolled. The primary efficacy analysis will be conducted no later than 12 months after the last subject received the first dose of study drug. Tumor response

will be assessed by investigator review according to 2014 International Working Group in NHL (Appendix 3). Patient will receive a PET and contrast CT at screening, after 12 and 24 weeks of therapy, and at suspected complete remission. Contrast CT alone will be performed at weeks 36, 48, and thereafter, once every 16 weeks. Response will be assessed on the basis of radiological evaluations. Complete responses should be confirmed by PET and contrast CT in all subjects, by endoscopy for any subjects with a documented history of gastrointestinal involvement, and by bone marrow biopsy in these subjects with bone marrow tumor involvement prior to study drug. Bone marrow biopsy has to be performed at screening.

All subjects will be followed for AEs for 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

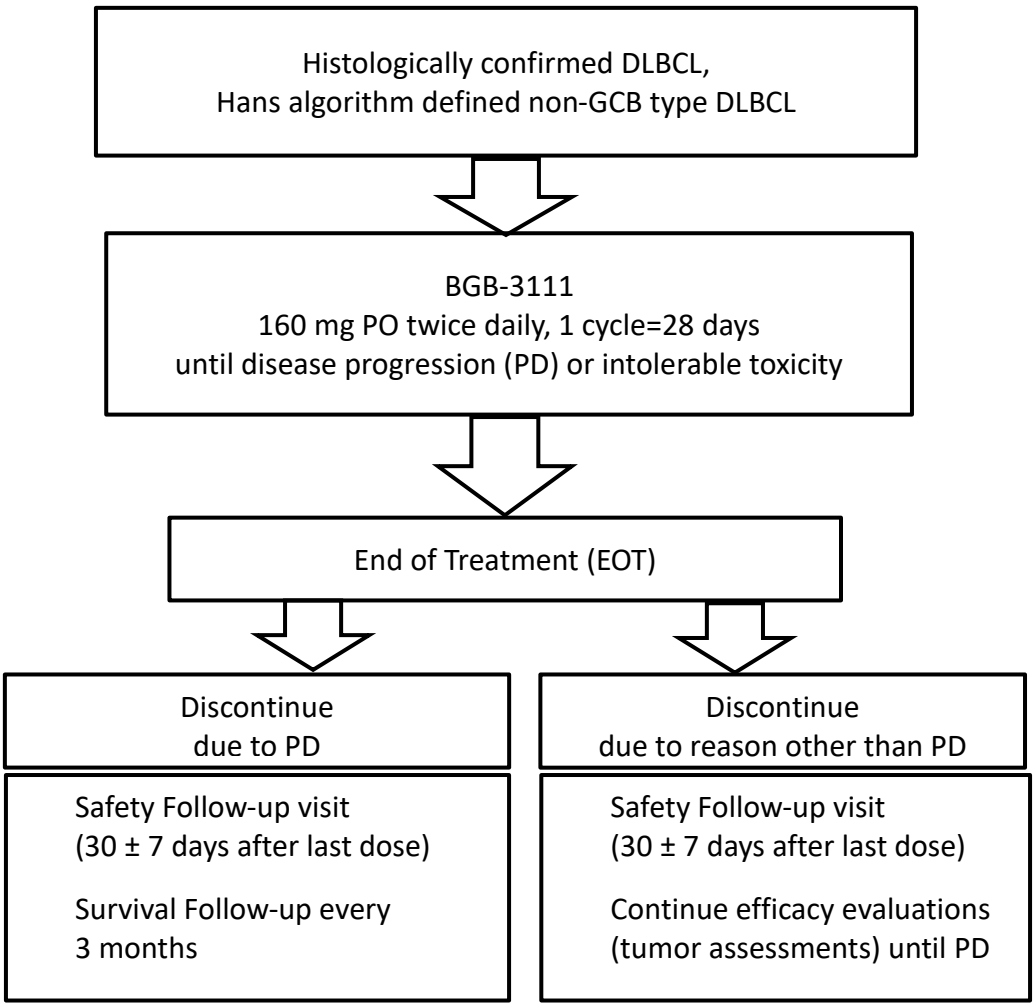
Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations. Please refer to Table 2 for details on screening procedures. Screening evaluations can be repeated within the screening period.

Treatment phase: All subjects will receive zanubrutinib 160 mg BID. All subjects in the study will be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. At the time of final analysis, subjects who remain on treatment will be considered for participation in the extension study when eligible. A treatment cycle consists of 28 days.

Follow-up phase: Subjects will return approximately 30 days after the last dose of study drug for safety follow-up visit. Assessments to be performed are presented in Table 2. Radiological assessments will continue until documented disease progression. If a subject discontinues study drug due to reasons other than disease progression, radiological assessments will continue until subject exhibits first progression, starts new anti-cancer therapy, withdrawal of consent, death, lost to follow-up or study termination by sponsor, whichever occurs first.

Survival phase: Subjects will be followed for survival via phone contact (with patient guardian, if applicable) every 3 months after the subject's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis.

Figure 1 Schema for Study BGB-3111-207



5 STUDY POPULATION

5.1 Inclusion Criteria

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

1. Histologically confirmed non-GCB DLBCL, by immunohistochemistry using the Hans algorithm,
   - CD10- and BCL6-
   - CD10- and BCL6+、but MUM1+
2. Men and women ≥18 years of age.
3. ECOG performance status of 0-2.
4. Measurable disease is defined as at least one lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions.
5. All subjects must provide fresh tumor biopsy or recent tumor tissue samples (within 2 years of study entry [informed consent form signed]).
6. Received at least one prior therapy for DLBCL that includes anthracycline based chemotherapy.
7. Patient not eligible for or refuses intensive chemotherapy and autologous bone marrow transplantation.
8. Documented failure to achieve at least PR with, or documented disease progression after response to, the most recent treatment regimen.
9. Neutrophils ≥ 1 x 10^9/L, independent of growth factor support within 7 days of first dose of study drug.
10. Platelets ≥ 75 x 10^9/L, independent of growth factor support or transfusion within 7 days of first dose of study drug.
11. Creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the modification of diet in renal disease [MDRD]).
12. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN).
13. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome, up to 5 x ULN).

14. Independent of erythropoietin (EPO) support or transfusion within 7 days of first dose of study drug

15. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN.

16. Subjects may be enrolled who relapse after autologous stem cell transplant, at least 6 months after transplant, subjects should have no active infections (ie, fungal or viral).

17. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control can be defined as abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for up to 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or utilize a barrier method where the female partner utilizes the effective forms of birth control noted above.

18. Life expectancy of > 3 months.

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

5.2 Exclusion Criteria

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

1. Current or history of CNS lymphoma.

2. Prior exposure to a BTK inhibitor.

3. Prior corticosteroids (at dosages equivalent to prednisone > 20 mg/day) given with anti-neoplastic intent within 7 days, prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, or antibody-based therapies or Chinese anti-cancer herbal therapies within 4 weeks of the start of study drug.

4. Major surgery within 4 weeks of screening.

5. Toxicity of ≥ Grade 2 from prior anti-cancer therapy (except for alopecia, absolute neutrophils, and platelets. For neutrophils and platelets, please following inclusion criteria #9 [neutrophils] and #10 [platelets]).

6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell

carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.

7. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or Class 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification, or history of myocardial infarction within 6 months of screening. Left Ventricular Ejection Fraction (LVEF) is lower than 50% measured by echocardiography (ECHO).

8. QTcF (Fredericia's correction) > 450 msecs or other significant electrocardiogram (ECG) abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block.

9. 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.

10. Uncontrolled systemic infection or infection requiring parenteral antimicrobial therapy.

11. Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR]).

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA<1000 IU/mL, After enrollment, check HBV DNA monthly or every 3 cycles for patients receiving anti-HBV medication to prevent HBV reactivation	HBsAg(-) HBcAb(+)	HBV DNA ≥1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA<1(log_{10}IU/mL), and monthly monitoring or treatment with anti-HCV medication.	Antibody(+)	HCV RNA ≥1(log_{10}IU/mL)

HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

HBV evaluation includes HBsAg, HBcAb, HBsAb. If subject is HBsAg- but HBcAb+ (without considering HBsAb status), will evaluate HBV DNA using PCR, the acceptable upper limit is 1000IU/ml, however, because different assays are used in different hospitals, the acceptable upper limit will be that of the upper limit at the hospital where the test is conducted. HCV evaluation involves the HCV Ab, if positive, to evaluate HCV RNA as above.

12. Pregnant or lactating women.

13. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk.

14. On medications which are strong CYP3A inhibitors or CYP3A inducers. See Section 6.6.2 for clarification on medications which are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or CYP3A inducers (Appendix 4).

6 STUDY TREATMENTS

6.1 Study Treatment

Subjects will receive zanubrutinib 160 mg (two - 80 mg white opaque capsules) orally twice daily (BID) with a minimum 8 hours between two consecutive doses.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

The capsule supplies of zanubrutinib will be provided in a child-resistant high density polyethylene (HDPE) bottle with induction seal and bottle label. The label will include at minimum, space to enter the subject number and name of investigator, content and quantity of zanubrutinib, protocol number, batch number, directions for usage, storage conditions, and cautions.

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

6.2.2 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.

Study drug must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug. All study drug must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug-specific

requirements. The study drug must be kept at the condition as specified on the labels, or according to the latest version of the IB.

6.2.3 Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each subject visit and information provided by the subject and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by subjects, if applicable.

6.2.4 Disposal and Destruction

After completion of the study, all unused zanubrutinib will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies will be returned to the sponsor or destroyed on site or depot, after receiving written sponsor approval.

6.3 Subject Numbering and Treatment Assignment

6.3.1 Subject Numbering

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned when the subject is screened or enrolled in the study. Subject will be assigned in chronological order starting with the lowest number. Once a subject number has been assigned to a subject, it cannot be reassigned to any other subject. Subject can be re-screened if the subject did not previously meet the inclusion and exclusion criteria. Re-screening is defined as repeating the screening procedures or tests within the original screening window. A new informed consent is not required and subject shall maintain the same subject number as originally assigned.

6.3.2 Treatment Assignment

All subjects in the study will receive zanubrutinib.

6.3.3 Treatment Blinding

This is an open-label study.

6.4 Dosage and Administration

Zanubrutinib will be dispensed by the study center personnel on Day 1 of each cycle (every 4 weeks) during the first year and Day 1 of every other cycle thereafter (every 8 weeks starting on cycle 13). Subjects will be provided with an adequate supply of study drug for self-administration at home. The investigator should instruct the subject to take the study drug exactly as prescribed. Subjects will be requested to bring their unused medication including empty packaging to the center at each visit. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib will be taken daily from Cycle 1 Day 1 until disease progression, unacceptable toxicity or death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Subjects will be advised that if a dose of the study drug is not taken at the scheduled time, they should take the missed dose as soon as they remember and return to the normal schedule for the next dose. Subjects should skip the missed dose if it is 4 hours or less to the next scheduled dose. An extra dose of the study drug should not be taken to make up for the missed dose.

6.5 Dose Interruption and Modification

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

Table 1 Zanubrutinib Dose Reduction Steps

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

BID= twice a day QD=once a day

Study drug may be held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the subject's best interest to restart treatment after more than 28 days, then written approval must be obtained from the sponsor medical monitor.

6.5.1 Dose Reductions for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting >7days, however, earlier interruption acceptable if medically indicated)
- Grade 4 thrombocytopenia (lasting >7days, however, earlier interruption acceptable if medically indicated)
- ≥Grade 3 febrile neutropenia
- ≥Grade 3 thrombocytopenia associated with bleeding

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. If the same event reoccurs, subjects will restart at one dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions will be allowed. Subjects with Grade ≥ 3 thrombocytopenia associated with significant bleeding requiring medical intervention will be discontinued from study treatment.

Asymptomatic treatment-related lymphocytosis should not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures. For fever associated with neutropenia, take medical history, perform physical examination, and the relevant imaging, and blood, body fluid cultures to ascertain cause of infection, and administer anti-infective therapy as per hospital guidelines. Growth factor use should be considered as per investigator judgement.

6.5.2 Dose Reductions for Non-Hematologic Toxicity

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

6.6 Concomitant Medications and Non-Drug Therapies

6.6.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication and dates of administration. Tumor Lysis Syndrome (TLS) has not been reported with zanubrutinib treatment, but has been reported rarely with ibrutinib. Subjects with high tumor burden should be

monitored closely and prophylactic measures, including allopurinol, may be instituted per institutional standards.

6.6.2 Prohibited Medications

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

Drugs known to prolong the QT/QTc interval are prohibited, in accordance with FDA Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. A link to a list of drugs with QTc prolongation potential is provided through the Arizona Center for Education and Research on Therapeutics (CERT; "Drugs That Prolong the QT interval and/or Induce Torsades de Pointes"): http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm and is provided in Appendix 2.

The primary metabolic pathway for zanubrutinib involves the CYP3A isoform. The compounds/substances presented in Appendix 4 are either strong CY3A4 inhibitors or inducers which are prohibited in the current study. When treatment with a strong CYP3A4 inhibitor or inducer becomes medically necessary during the study, and an acceptable alternative medication is not available, consultation with the sponsor medical monitor is required. Subjects are allowed to take moderate CY3A4 inhibitors but need to be closely monitored. Please refer to the drug-drug interaction (DDI) database from Indiana University, the University of Washington, and FDA for more information.

6.6.3 Medications to be used with Caution

Zanubrutinib is a moderate inhibitor of human CYP isoenzyme CYP2C8 (IC_{50} = 4.03 μM), CYP2C9 (IC_{50} = 5.69 μM), and CYP2C19 (IC_{50} = 7.58 μM). Although unlikely to reach the drug concentration that could cause significant inhibition of these CYP enzymes in clinic, investigators should be aware that zanubrutinib has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C8, CYP2C9, and CYP2C19. Examples of these medications include, but are not limited to those listed in Appendix 5 and these should be used cautiously with the monitoring of drug concentrations where appropriate. Please refer to the DDI database from Indiana University, the University of Washington, and FDA for updated information and Appendix 5.

6.7 Discontinuation of treatment and premature withdrawal

When the study drug is permanently discontinued regardless of reason, the subject will have an End of Treatment (EOT) visit within 7 days of stopping study drug. A visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed (see Table 2). The reason for discontinuation from treatment will be recorded on eCRF.

6.7.1 Discontinuation of treatment

Subjects may discontinue study drug for one of the following reasons:

- Death
- Disease progression
- Adverse event(s)
- Pregnancy
- Drug interruption >28days
- Subject withdrew consent

All subjects who discontinue study drug will have a safety follow-up visit approximately 30 days after the last dose of study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the 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 will only be performed if the subject had an ongoing laboratory abnormality at the previous visit which the investigator considered to be related to study drug. If the subject is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the subject or caregiver to collect this information.

Subjects who are discontinued from study drug for any reason (i.e. AE or administrative reasons etc.) other than disease progression should not be considered withdrawn from the study. They will continue to be followed for efficacy evaluations per protocol schedule until subject exhibits first progression, starts new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them or retrieve information by telephone to determine the subject's disease status and survival.

Subjects may voluntarily withdraw from the study (i.e. withdraw consent) or be dropped from it at the discretion of the investigator at any time. Subjects lost to follow up should be recorded as such on the CRF. For subjects who are lost to follow-up, the investigator should demonstrate "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

6.7.2 Early Termination

- Study termination by sponsor
- Protocol violation
- If zanubrutinib is on market, sponsor can transfer patient onto marketed drug

- Lost to follow-up

7 STUDY ASSESSMENTS

7.1 Study Flow and Visit Schedule

The study-specific assessments and procedures are shown in Table 2.

Table 2 Study Assessment and Procedure Schedule for Study BGB-3111-207

	Pre-treatment	Treatment All cycles are 28 days (4 weeks) in duration				End of Study Assessments		
	Screening	Cycle 1	Cycle 2	Cycle 3 to Cycle 13 (Every 4 weeks)	Cycle 15, Cycle 17, Cycle 19, etc… (Every 8 weeks)	EOT	Safety Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (+/- 3 days)**	**Day 1 (+/- 3 days)**	**Day 1 (+/- 7 days)**	**(Within 7 days after stopping treatment)**	**30 ± 7 days after last dose of study drug**	**Every 3 months ± 7 days**
Visit	0	1	2	3, 4, 5, etc.…				
Informed consent	X [2]							
Inclusion/exclusion criteria	X [3]							
Demography	X [4]							
Medical/surgical history/current medical conditions	X [5]							
Diagnosis and extent of cancer	X [6]							
Prior antineoplastic therapy	X							
12-lead ECG [7]	X[7]	X [7]				X		
Lipid panel	X [8]							
ECOG performance status	X	X	X	X	X	X	X	
Height (in cm)	X							
Weight (in kg)	X	X	X	X	X	X	X	
Vital signs and physical examination (including assessment of B symptoms and liver and spleen enlargement)	X [9]	X	X	X	X	X	X	
Hematology [10]	X	X	X	X	X	X		
Chemistry [10]	X	X	X	X	X	X		
Coagulation [10]	X	X						
Urinalysis (macroscopic; microscopic if required) [10]	X	X	X	X	X	X		
Hepatitis B/C testing and HIV testing [10]	X							
Urine or serum pregnancy test (if applicable)	X[10]	X	X	X	X	X		

	Pre-treatment	Treatment All cycles are 28 days (4 weeks) in duration				End of Study Assessments		
	Screening	Cycle 1	Cycle 2	Cycle 3 to Cycle 13 (Every 4 weeks)	Cycle 15, Cycle 17, Cycle 19, etc… (Every 8 weeks)	EOT	Safety Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (+/- 3 days)**	**Day 1 (+/- 3 days)**	**Day 1 (+/- 7 days)**	**(Within 7 days after stopping treatment)**	**30 ± 7 days after last dose of study drug**	**Every 3 months ± 7 days**
Study drug administration [11]		X	X	X	X			
Bone marrow biopsy/aspiration [12]	X	At time of CR						
Endoscopy [13]		At time of CR						
Echocardiogram[14]	X							
Imaging [15]								
PET+contrast CT scan	X	At week 12, week 24, and at time of CR						
CT scan with contrast of neck/chest/abdomen and pelvis (or MRI)	X	At week 36 and week 48, then every 16 weeks after week 48						
Brain CT/MRI scan with contrast	As clinically indicated							
Concomitant medications	Throughout							
AEs/SAEs	Throughout							
Antineoplastic therapies since discontinuation of study drug							X [16]	X [16]
Survival follow-up [17]								X
Tumor tissue collection for biomarkers [18]	X							

Abbreviations: AEs: adverse events; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: End of Treatment; MRI: magnetic resonance imaging; PET: positron emission tomography; SAEs: serious adverse events; X: to be performed

Windows: days allowed for reschedule of an entire visit due to logistical reasons (eg, Public Holidays). These are: ECOG, weight, vital signs, physical examination (including B symptoms), hematology, clinical chemistry, lipid panel, urinalysis, concomitant medications, AEs/SAEs, pregnancy test, and study drug administration.

Assessments scheduled on Cycle 1 Day 1 should be performed prior to the administration of the first dose of zanubrutinib. Screening blood and urine tests performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

1. Screening evaluations will be performed and completed within 28 days prior to the first dose of zanubrutinib. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Cycle 1 Day 1.
2. Written informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
3. The investigator will review and ensure that the subject meets all of the inclusion and none of the exclusion criteria.
4. Demography includes gender and date of birth (or age).
5. Relevant medical history (ie. previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility, and current medical conditions.
6. Other background information including history of disease and current disease status, staging, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.
7. Perform a 12-lead ECG in triplicate at screening and EOT. Subjects should be in the semi-recumbent or supine position.
8. Lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides performed at screening only.
9. A complete or targeted physical examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified. Complete physical exam includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes /spleen, skin, oropharynx, and extremities. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. Clinical suspicion of disease progression at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats. If the physical examination is not completed +/- 7 days of the radiological tumor assessment, a separate physical examination should be performed.
10. Laboratory assessments include the following:
    a. Screening laboratory tests performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.
    b. Hematology, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, absolute differential count

(neutrophils, eosinophils, lymphocytes, monocytes, basophils, blasts) and platelet count. In the event of neutropenia (absolute neutrophil count < 1000/mm^3) or thrombocytopenia (platelets of less than 75,000/mm^3), these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2 or baseline (ANC ≥ 1000/ mm^3).

c. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, fasting glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphate, magnesium, total bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2.

d. Coagulation profile will be performed at screening and Cycle 1 Day 1, and includes activated partial thromboplastin time (APTT) (screening only) and prothrombin time (PT), which will also be reported as international normalized ration (INR).

e. Hepatitis B/C serologic markers and viral load will be tested. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by PCR if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). If HBV DNA is lower than 1000 IU/mL or normal value, subjects will be enrolled and screened for HBV DNA every month or every 3 cycles for patients receiving anti-viral therapy. The hepatitis C testing includes Hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. If HCV RNA is lower than normal value, subjects will be enrolled and screened for HCV DNA every month or take anti-viral therapy. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

f. Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes pH, glucose, and protein. If urine protein is ≥2+ by dipstick, a 24-hour urine for total protein and creatinine will be obtained and evaluated.

g. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

11. Subjects will receive zanubrutinib at a dosage of 160 mg (two - 80 mg white opaque capsules) orally twice daily. Zanubrutinib will be administered on a 28-day cycle and will continue until disease progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study for any reason. All subjects will have an end of treatment (EOT) visit within 7 days after stopping study drug. All subjects will have a follow-up visit 30 ± 7 days after the last dose of the study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
12. A bone marrow aspiration and biopsy must be performed at screening for all subjects if not performed within 60 days of first dose. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible CR (eg, physical exam or CT scan indicating a possible

CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR.

13. Gastrointestinal endoscopy must be performed to confirm CR for any subject with a documented history of gastrointestinal involvement.
14. An echocardiogram to be performed at screening; an echocardiogram performed within 30 days of first dose can be substituted.
15. CT scans should encompass neck, chest, abdomen, and pelvis and include oral and intravenous contrast. A brain scan is required if clinically indicated. In all cases, an MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study. Tumor response will be assessed according to 2014 International Working Group in NHL (Appendix 3). Tumor assessment by PET and contrast CT scan at screening, 12 weeks, and 24 weeks will be performed. If subjects do not have PET-avid disease at screening, contrast CT will be performed after screening. Subjects will be performed contrast CT scan at week 36 and week 48; thereafter, contrast CT scan every 16 weeks until disease progression or end of study, whichever comes first. Complete response should be confirmed by PET and CT for subjects who had PET-avid disease during screening. In subjects with bone marrow tumor involvement prior to study drug, CR should be confirmed by bone marrow biopsy. Unscheduled response assessments may be performed based on physical examination or laboratory findings, at the discretion of the investigator. Clinical suspicion of disease progression at any time will require radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.
16. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
17. Survival information will be collected via telephone call every 3 months ± 7 days after the subject's last visit until after the subject's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
18. For all subjects, fresh tumor biopsy or recent tumor tissue samples (within 2 years of study entry) will be collected. Either a formalin-fixed paraffin-embedded block with tumor tissue or at least 10 unstained slides (5 μm) should be sent to the central laboratory for genetic biomarker analysis. For subjects without sufficient tumor samples for genetic biomarker analysis, tumor tissue biopsy can be used as replacement. For subjects with accessible tumor site and in agreement with tumor tissue biopsy, tumor tissue biopsy will be performed at screening. The detailed information of tumor tissue collection will be described in lab manual.

7.2 Subject Demographics/Other Baseline Characteristics

7.2.1 Demography

Demographic data will include gender, date of birth (or age), and race/ethnicity.

7.2.2 Medical History

Medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility will be collected and captured in the eCRF.

7.2.3 Other Baseline Characteristics

Other background information including history of disease and current disease status, staging (Table 3), bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.

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

Table 3 Revised Ann Arbor Staging Classification[a]

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

[a] Cheson et al, 2014

7.3 Efficacy

Response will be evaluated using the 2014 International Working Group in NHL criteria (Appendix 3).

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 2, based on physical examination, radiological assessment and bone marrow biopsy (to confirm complete responses in subjects with bone marrow tumor involvement prior to study drug). Tumor assessment by PET and CT (with contrast) at screening, 12 weeks, and 24 weeks will be performed. CT (with contrast) will be performed at week 36 and week 48, and thereafter, every 16 weeks until disease progression or end of study, whichever comes first.

Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline.

Complete responses should be confirmed by positron emission tomography (PET) and contrast CT in subjects who had PET-avid disease at screening, by endoscopy for any subjects with a documented history of gastrointestinal involvement, and by bone marrow biopsy in these subjects with bone marrow tumor involvement prior to study drug.

7.3.1 Physical Examination

Evaluation of disease related B symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months) and enlargement of liver and spleen is included in the physical examination at each visit. If the physical examination is not completed ± 7 days of the radiological tumor assessment, a separate physical examination should be performed.

7.3.2 Radiological Tumor Assessment

Baseline radiological tumor assessment should be performed within 28 days of the first dose.

Tumor assessment by PET and CT (with contrast) at screening, 12 weeks, and 24 weeks will be performed. CT (with contrast) will be performed at week 36 and week 48, and thereafter, every 16 weeks until disease progression or end of study, whichever comes first. Complete responses should be confirmed by positron emission tomography (PET) and contrast CT in subjects who had PET-avid disease at screening, by endoscopy for any subjects with a documented history of gastrointestinal involvement. CT of the brain is only indicated if clinical findings or symptoms

suggest CNS involvement. Subjects will be treated by the investigator according to the local radiologist's assessments.

A CT scan of diagnostic quality performed as part of PET/CT is required, provided bi-dimensional nodal and liver/spleen measurements can be made. An MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study.

All CT scans, MRIs, PET scans, and PET/CT scans obtained during the study will be collected and archived. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, central imaging vendor).

7.3.3 Bone Marrow Assessment

A unilateral bone marrow aspirate and biopsy must be performed at screening if not performed within 60 days of the first dose for all subjects, provided there has been no intervening therapy between the time of the biopsy and start of study drug. In those subjects who had evidence of bone marrow disease at screening, upon achieving a possible CR (eg, physical exam or CT scan indicating a possible CR), a bone marrow aspirate and biopsy should be obtained to confirm the CR.

Testing will be performed at the study center's local laboratory. De-identified copies of all bone marrow biopsy/aspirate results must be provided to the sponsor or designee.

7.3.4 Endoscopy

Gastrointestinal endoscopy must be performed to confirm CR for any subject with a documented history of gastrointestinal involvement.

7.4 Safety

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 2.

7.4.1 Adverse Events

All AEs and SAEs, regardless of the relationship to the study drug, will be collected from the time of subject informed consent. All subjects will be followed for safety 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or

stabilization. The accepted regulatory definition for an AE is provided in Section 9.1. Important additional requirement for reporting SAEs are explained in Section 9.2.

7.4.2 Physical Examination, Vital Signs, Height, and Weight

A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), weight, and B symptoms examination will be performed at each study visit. Height (cm) is determined at screening/baseline only. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats.

A complete physical exam includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. A targeted physical exam will be at all visits except where a complete physical exam is required for screening/baseline.

If the physical examination is not completed ± 7 days of the radiological tumor assessment, a separate physical examination should be performed.

7.4.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, each visit during study treatment, and at End of Treatment Visits. Appendix 6 will be used to assess performance status.

7.4.4 Echocardiogram

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

7.4.5 Laboratory Evaluations

Laboratory assessments should be performed at a local certified laboratory. Clinical chemistry, hematology, coagulation and urinalysis will be performed at the time points specified in Table 2, and may also be performed as medically necessary. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and urine tests were

performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

7.4.5.1 Hematology

Hematology includes hemoglobin, hematocrit, reticulocyte, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils. In the event of neutropenia (absolute neutrophil count < 1,000/mm^3) or thrombocytopenia (platelets of less than 75,000/mm^3), these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2 baseline (ANC sm 1,000/ mm^3).

7.4.5.2 Clinical Chemistry

Clinical chemistry includes albumin, alkaline phosphatase, AST, ALT, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, fasting glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2.

7.4.5.3 Serum Lipid Profile

Lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides will be performed at screening only.

7.4.5.4 Coagulation

The coagulation profile includes APTT (screening only) and prothrombin time (PT), which will also be reported as international normalized ratio (INR). The coagulation profile will be performed at screening and on Cycle 1 Day 1.

7.4.5.5 Urinalysis

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If urine protein is ≥2+ by dipstick, a 24-hour urine for total protein and creatinine will be obtained and evaluated**.**

7.4.5.6 Pregnancy test

A serum pregnancy test will be performed at screening and end of treatment in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A subject who has a positive pregnancy

test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

7.4.5.7 Hepatitis B/C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes Hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible. Subjects HBsAg negative, HBcAb positive and HBV DNA negative must undergo monthly HBV DNA screening PCR. Subjects positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA screening. Subjects with known HIV are excluded from the study.

Table 4 shows how the results for HIV, HBV, and HBV testing at screening relate to inclusion and exclusion criteria

Table 4 HBV, HCV, and HIV Testing for Inclusion/Exclusion

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA<1000 IU/mL, Monitor monthly, or initiate anti-HBV therapy。	HBsAg(-) HBcAb(+)	HBV DNA≥1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA<1 (log_{10}IU/mL), monitor monthly, or anti-HCV therapy	Antibody(+)	HCV RNA≥1 (log_{10}IU/mL)

7.4.6 Electrocardiogram

Perform a 12-lead ECG in triplicate at screening and EOT. Subjects should be in the semi-recumbent or supine position.

7.5 Biomarkers

7.5.1 Predictive Biomarkers

For all subjects, fresh tumor biopsy or recent tumor tissue samples (in 2 years) will be collected. Either a formalin-fixed paraffin-embedded block with tumor tissue or at least 10 unstained slides (5 μm) should be sent to the central laboratory for genetic biomarker analysis. For subjects without sufficient tumor samples for genetic biomarker analysis, tumor tissue biopsy can be used as replacement. For subjects with accessible tumor site and in agreement with tumor tissue biopsy,

tumor tissue biopsy will be performed at screening. The detailed information of tumor tissue collection will be described in lab manual.

7.6 Appropriateness of Measurements

All safety assessments used in this study are standard, ie, are widely used and generally recognized as reliable, accurate, and relevant.

8 DATA HANDLING AND QUALITY ASSURANCE

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

8.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by International Conference on Harmonisation (ICH) guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

8.2 Data Management/Coding

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

The Data Management Plan defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure that data are properly entered, validated, coded, integrated, reconciled, and reviewed.

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

8.3 Quality Assurance

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

9 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol. All AEs and SAEs, regardless of the relationship to the study drug, will be collected from the time of subject informed consent, and until resolution or stabilization of all study drug related AEs.

9.1 Adverse Events

9.1.1 Definitions and Reporting

An AE is an untoward medical occurrence in a clinical investigational subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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 a study drug.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- 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.
- Significant failure of expected pharmacological or biological action.

Examples of an AE do not include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. Adverse events are independent components of the study.

9.1.1.1 Period and Method of Detecting AEs and SAEs

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

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

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?

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

9.1.1.2 Assessment of Severity

The investigator will make an assessment of 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 v4.03.

9.1.1.3 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 event to the study drug will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

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

Investigators must also systematically assess the causal relationship of AEs to IMP(s)/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions.

- **Definitely related:** There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (When necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment.
- **Probably related:** This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study treatment that: There is reasonable temporal relationship; the occurrence of AE could not be explained by the subject's medical history, concurrent medical condition, or other the subject's signs or symptoms; the positive of de-challenge result; the positive of re-challenge result;
- **Possibly related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Unlikely related:** There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.
- **Not related:** An adverse event will be considered "not related" to the use of the product if any of the following tests are met:

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

9.1.1.4 Follow-Up of Adverse Events and Serious Adverse Events

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

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

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other 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 subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be resent to the sponsor within the time frames outlined in Section 9.2.2.1.

9.1.2 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, hematology, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, X-rays, vital signs, etc.) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 9.1) or an SAE (as defined in Section 9.2). Clinically significant abnormal

laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

9.1.2.1 Post-study Adverse Events and Serious Adverse Events

A post-study AE or SAE is defined as any event that occurs outside of the AE/SAE detection period, defined in Section 9.1.1.1

Investigators are not obligated to actively seek AEs or SAEs in former subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor or designee.

9.1.3 AE due to disease progression

Adverse events that are clearly consistent with the expected picture of progression of the underlying disease (e.g., new metastases or transformation to more aggressive histology) should **NOT** be recorded as adverse events. They should be recorded on CRF as efficacy data, not reported as adverse events.

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

9.1.4 Adverse Events Secondary to Prior Events

A medically significant secondary adverse event that is a clinical sequelae of a prior event should be reported as an independent event. For example, if a patient has an initial adverse event of cough and a few days later the patient develops pneumonia, both events should be reported separately on the CRF. If a patient has neutropenia that is followed by a subsequent infection, both events should be reported separately. The start date of the former event should be the onset date for that event. The start date of the subsequent event should be the onset date for the subsequent event.

If it is unclear as to whether the events are interrelated, all events should be reported separately on CRF.

9.1.5 Recurrent Adverse Events

A recurrent adverse event is an event that resolves and subsequently recurs. All recurrent events should be reported separately on CRF.

9.1.6 Death

Death is an outcome of an adverse event and the adverse term "death due to {condition}" should NOT be reported as an adverse event. Deaths that occur during the adverse event reporting period that are assessed by the investigator as solely to disease progression should be recorded on Study Completion or Early Discontinuation CRF. They should not be reported as adverse events. If deaths are attributed by the investigator not solely due to disease progression, whether they are assessed as related or not related to the study drug, they should be reported as serious adverse events as per the timeline stipulated in the 8.2.2.1 timeframes for Submitting Serious Adverse Event. If deaths occur outside of the adverse event reporting period, the investigator will promptly notify the sponsor according to descriptions provided in Section 9.1.2.1.

9.2 Serious Adverse Events

9.2.1 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 subject 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 subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

- 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 (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Disease progression should not be reported as an AE/SAE, but symptoms meeting the definition of, and associated with, disease progression should be reported.

9.2.2 Reporting

9.2.2.1 Timeframes for Submitting Serious Adverse Events

Serious adverse events will be reported promptly to the sponsor as described in Table 5 once the investigator determines that the event meets the protocol definition of a SAE.

Table 5 Timeframe for Reporting Serious Adverse Events to the Sponsor

Type of SAE	Initial SAE Report	Document	Follow-up SAE Report	Document
All SAEs	24 hours of investigator's knowledge	SAE report form/eCRF	ASAP	Updated SAE report form/eCRF

SAE: serious adverse event; eCRF: electronic case report form

9.2.2.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.2.2.1. The SAE report form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to the sponsor within the designated timeframes. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.1.2.

Facsimile transmission of the SAE report form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE report form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE report form within the time frames outlined in Section 9.2.2.1.

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

The following pages of the eCRF must accompany the SAE report forms that are forwarded to the sponsor: “demography”, “medical history”, “concomitant medications”, “study medication records”, and “death form” (if applicable).

9.2.2.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.2.2.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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

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

Expedited investigator safety reports are prepared according to the sponsor’s policy and are forwarded to investigators as necessary. Such a report is prepared for an SAE that is both attributable to study drug and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

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

9.2.2.4 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests), even if it occurs during the post-treatment period, will be reported promptly to the sponsor (Section 9.2.2.2).

9.3 Pregnancies

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

9.3.1 Time Point for Collecting Pregnancy Information.

The time points for collecting information on whether a pregnancy occurs is from Screening until 30 days after the last investigational product administration. Information on pregnancies identified prior to the investigational product administration does not need to be reported to sponsor.

9.3.2 Action to be Taken and Reporting if a Pregnancy Occurs

A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

The Investigator, or his/her designee, will collect pregnancy information on any female subject or a female partner of a male subject who becomes pregnant while participating in this study. The Investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of a subject's or male subject's female partner's pregnancy. The subject or male subject's female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor.

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

A spontaneous abortion is always considered to be an SAE. Furthermore, any SAE occurring because of a post-study pregnancy and is considered reasonably related to the study drug by the Investigator, will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

9.4 Lack of Efficacy

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

9.5 Safety Monitoring Committee

All enrolled subjects 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).

Subjects will be evaluated for AEs (all grades, according to NCI CTCAE v.4.03) and serious AEs. Subjects who, at time of progression, have an ongoing AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable; the subject is lost to follow-up, or the subject starts a different anti-tumor therapy.

A Safety Monitoring Committee (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. This early safety review will occur about 3 months after enrollment of the 25th subject. No recruitment stop is planned for this interim safety review. At the safety review, special attention will be paid to significant safety events (SSE). Subsequent safety data review is outlined in SMC charter.

A SSE is defined as any of the following:

- General toxicity (NCI CTCAE v.4.03): Grade 3 and Grade 4 AEs and SAEs
- Any adverse event that requires dose interruption, reduction or discontinuation of the study drug.
- A subject's death

In the case of major toxicity concerns, the SMC can recommend to modify the trial conduct.

10 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) according to sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

10.1 Primary, Secondary and Exploratory Study Endpoints

10.1.1 Primary Endpoint

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or complete response (CR) by the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson et al 2014) (Appendix 3) at any time on study drug.

10.1.2 Secondary Endpoints

Efficacy:

- Progression free survival (PFS): defined as time from first dose of zanubrutinib until first documentation of progression (by IWG on NHL criteria) or death, whichever comes first.
- Duration of response (DOR) is defined as the time from the date that the response criteria are first met to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.
- Time to response (TTR) is defined as the time from first dose of zanubrutinib to documentation of a response.

Safety: To evaluate the safety and tolerability of zanubrutinib, as defined by:

- The incidence and severity of treatment-emergent adverse events (TEAEs), SAEs and treatment-related AEs according to NCI CTCAE v4.03
- The incidence, severity, and causation of adverse events leading to study drug discontinuation.

10.1.3 Exploratory Endpoints

[redacted]

[redacted]

10.2 Statistical Analysis

10.2.1 Analysis Populations

The Safety Population includes all subjects who received any dose of zanubrutinib. It will be the population for the efficacy and safety analyses.

The Per-Protocol Population (PP) includes subjects who received any dose zanubrutinib and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analyses.

10.2.2 Subject Disposition

The number of subjects enrolled, treated, prematurely discontinued from study drug (defined as those who discontinued study drug due to any reason except for progressive disease) and those with major protocol deviations will be counted. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF. The end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

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

10.2.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in safety population using descriptive statistics. 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, DLBCL IPI, and Ki67.

10.2.4 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 ± 7 days after the

subject's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

10.2.5 Efficacy Analyses

10.2.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is overall response rate (ORR) as determined by investigator review using the 2014 International Working Group in NHL criteria (Appendix 3). ORR is defined as the proportion of subjects achieving a best overall response of CR or PR.

The ORR in this study is estimated as 35%, which is deemed a clinical meaningful improvement.

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate. No hypothesis testing will be done.

Best overall response (BOR) is defined as the best response recorded from the start of zanubrutinib until data cut or start of new anti-neoplastic treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, stable disease [SD], and progressive disease [PD]) will be presented.

The primary efficacy analysis will be conducted approximately 12 months after the first dose of the last subject, and will be based on the safety population.

10.2.5.2 Secondary Efficacy Analysis

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

Kaplan-Meier (KM) 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 subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula.

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

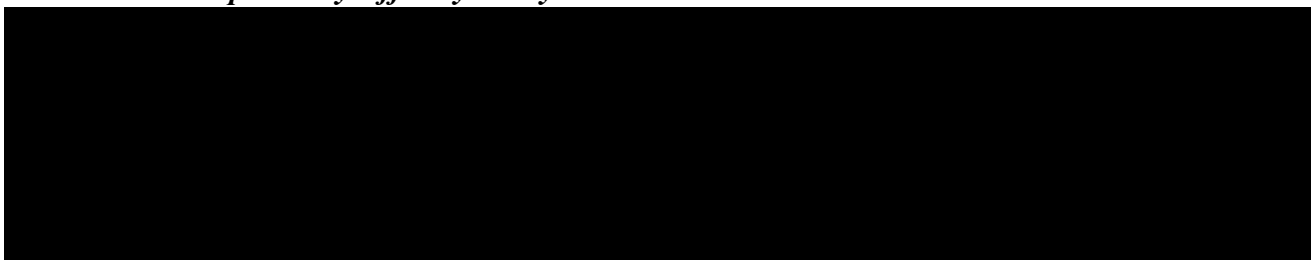
Duration of response (DOR) is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. Subjects who do not have disease progression will be censored at their last valid assessment. Time to response (TTR)

is defined as time from the starting date of zanubrutinib to the date the response criteria are first met.

Time to event variables (DOR and TTR) will be similarly analyzed using the KM method as described above. The KM estimates of DOR and TTR will be plotted over time.

Sensitivity analysis will be performed for primary and secondary endpoints in the PP population.

10.2.5.3 Exploratory Efficacy Analysis



10.2.5.4 Subgroup Analysis

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: sex, age group (≥60), disease stage, ECOG-PS (0 vs. ≥1), number of prior lines of therapy, IPI (<3 vs. ≥3), bulky disease (> 7.5 cm). Within group values (rates or means/medians) will be presented in forest plots.

10.3 Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI CTCAE v4.03. Laboratory values (hematology, clinical chemistry, coagulation, and urinalysis), vital, physically examine and ECGs findings will also be used in determining the safety. Descriptive statistics will be used to analyze all safety data in the safety population.

10.3.1 Extent of Exposure

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

The number (percentage) of subjects 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.

10.3.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug up to 30 ± 7 days following study drug discontinuation or was worsening in severity from baseline (pretreatment). Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to NCI CTCAE v4.03 within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship. Serious adverse events, deaths, TEAE with grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

10.3.3 Laboratory Analyses

Clinical laboratory (ie, hematology, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter by subject. 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 NCI CTCAE v4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in

both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

10.3.4 Vital Signs

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

10.3.5 Electrocardiogram

Electrocardiogram assessments will be performed at the Screening visit. Descriptive statistics for baseline ECG parameters will be presented.

10.4 Sample Size Consideration

Approximately 40 subjects will be enrolled.

The sample size calculation was based on the level of precision of the estimated ORR. Assuming an ORR of 35%, the 95% exact confidence interval will be 20.6% to 51.7%.

10.5 Interim Analysis

No interim analysis is planned in this study.

10.6 Other Statistical Issues

Not applicable.

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to 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" ICH guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

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

11.2.2 Ethical Conduct of the Study and Ethics Approval

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

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

the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

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

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

11.2.5 Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, 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 subjects screened and for all subjects enrolled in the trial.

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

11.2.6 Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.2.7 Drug Accountability

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

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

11.2.8 Inspections

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

11.2.9 Protocol Adherence

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

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by BeiGene. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.3.2 Study Report and Publications

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

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s).

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

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

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

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with BeiGene's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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

11.4 Study and Study Center Closure

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

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

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

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

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

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

11.5 Records Retention and Study Files

11.5.1 Study Files and Retention of Records

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) subject clinical source documents.

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

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

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

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

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

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

Biological samples at the conclusion of this study may be retained in storage by the sponsor for a period up to 1 year for purposes of this study.

11.6 Provision of Study Results and Information to Investigators

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

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

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

11.7 Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

11.8 Joint Investigator/Sponsor Responsibilities

11.8.1 Access to Information for Monitoring

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

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

11.8.2 Access to Information for Auditing or Inspections

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

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13 APPENDICES

Appendix 1 Signature of Investigator

PROTOCOL TITLE: A Phase 2, Single arm, Multicenter, Open-label Study of Bruton's Tyrosine Kinase (BTK) inhibitor BGB-3111 in subjects with relapsed/refractory non-GCB type Diffuse Large B cell lymphoma

PROTOCOL NO: BGB-3111-207

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Appendix 2 Medications which are known to prolong the QT interval and/or induce Torsades de pointes to be avoided

Antiarrhythmics
amiodarone
disopyramide
dofetilide
flecainide
ibutilide
procainamide
quinidine
sotalol
Anticancer
arsenic trioxide
vavdetanib
Antihistamines
astemizole
terfenadine
Antibiotics
azithromycin
clarithromycin
erythromycin
moxifloxacin
sparfloxacin
Antianginal
bepridil
Antimalarial
chloroquine
halofantrine
Antipsychotics
chlorpromazine
haloperidol
mesoridazine
pimozide
thioridazine
Antinausea
domperidone
droperidol
dolasetron (intravenous and oral)
Anti-infective
pentamidine

Antilipemic probucol
Antidpressants citalopram
Opiate agonists levomethadyl methadone
GI stimulant cisapride

Appendix 3 Revised criteria for response assessment of lymphoma (Cheson et al)

Response assessment will be performed according to the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria.

Positron emission tomography-computed tomography (PET-CT) should be used for response assessment in fluorodeoxyglucose (FDG)-avid histologies (using the 5-point scale provided in the footnote of the table); computer tomography (CT) is preferred for low or variable FDG avidity.

Revised criteria for response assessment classification Non-Hodgkin lymphoma at a given evaluation time point

Response and site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5-point scale [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete mediastinum 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 extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5[b] 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 extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	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 response	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses Extranodal lesions	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	PPD progression: An individual node/lesion must be abnormal with: LDi > 1,5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions> 2 cm In the setting of splenomegaly[c], the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If not prior splenomegaly, must increase by at least 2 cm from baseline
		New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transvers diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

a A score of 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 undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs). GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow). FDG uptake may be greater than the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5-point scale:
1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum; 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.

c Splenomegaly = vertical spleen length > 13 cm (reference: Cheson, BD et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32:3059–3068).

Appendix 4 Prohibited Medications (CYP3A Inhibitors and CYP3A Inducers)

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

Appendix 5 Medications to be Used with Caution

Medications are sensitive CYP2C8, CYP2C9, and CYP2C19 substrates or CYP2C8, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index.

CYP2C8 Substrates	**CYP2C9 Substrates**	**CYPC19 Substrates**
repaglinide[1]	celecoxib	**Anti-epileptics:**
paclitaxel	phenytoin[2]	S-mephenytoin[1,2]
	warafarin[2]	
		Proton Pump Inhibitors
		lansoprazole[1]
		omeprazole[1]

[1] Sensitive substrates: Drugs that exhibit an area under the plasma concentration-time curve (AUC) ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

Appendix 6 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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
As published by Oken MM, et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.	