BGB-3111 Protocol of a Chinese Phase I Clinical Study

Protocol Title:	**A phase I clinical study to investigate the safety, tolerability and pharmacokinetics/ pharmacodynamics of BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma**
Protocol No.:	**BGB-3111-1002**
Version No. & Date:	**Version 2.0, February 06, 2017**
Study Phase:	**Phase I**
Sponsor:	**BeiGene (Beijing) Co., Ltd**
Principal investigator:	[redacted]
Sponsor's Medical Monitor:	[redacted]

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SIGNATURE

PROTOCOL TITLE: **A phase I clinical study to investigate the safety, tolerability and pharmacokinetics/ pharmacodynamics of BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma**

PROTOCOL NO: BGB-3111-1002

SPONSOR:

Sponsor: BeiGene (Beijing) Co., Ltd

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Signature by Sponsor Representative Date

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Investigator

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Principal investigator (printed name)

AMENDMENT (VERSION 2.0) (FEB.6TH, 2017)

The overall reasons for this revision include updating the program based on ethical advice and newly obtained information from the centers; and making minor changes.

Section No.	Description of Change
Rationale: Based on the effectiveness data of BGB-3111 in global trials, the treatment period is extended to three years.	
Protocol synopsis 4.1 Overall design Table 3, Footnote 2 5.5.1 Completion of Study 6.2 Dosage & Administration 11.2.2 Study analysis Table 3: Study Assessments and Procedures Schedule. Annex 5: Flowchart	The original treatment period is one year, and the revised treatment period is extended to three years. Study duration includes screening (28 days); treatment period up to 3 years or until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination by the sponsor, whichever occurs first; safety follow-up (until 30 days after the last dose); survival follow-up until study completion. Moreover, In Table 3, we added items to be checked after one year and its frequency, as well as safety follow-up and survival follow-up.
Rationale: To avoid confusion, principle investigator was changed to lead investigator.	
Signature page Protocol synopsis 4.1 overall design	To avoid confusion, principle investigator was changed to leading investigator.
Rationale: To further explore the anti-tumor activity of BGB-3111 in an indolent lymphoma, we add dose expansion study as Part II. The number of patients to be enrolled has been increased from about 20 to about 40.	
Protocol synopsis 1.6 Clinical efficacy of BTK inhibitors in indolent lymphoma 2 Study Objectives 3 Study Endpoints 4 Study Plan 5.1 Inclusion Criteria 11 Statistical methods and analysis Table 3: Study Assessments and Procedures Schedule. Table 5: Pharmacokinetic	The clinical results of Phase I trials in Australia show that BGB-3111 has a very good efficacy in B-cell malignancy subjects, especially in subjects with chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom macroglobulinemia. When BGB-3111 completes the safety assessment in B lymphocytic tumors in Chinese subjects and determines the recommended dose for Phase II trials, Phase II trials of multiple indications will be followed. For patients with follicular lymphoma and marginal lymphoma, BGB-3111 also showed preliminary efficacy, but due to the limited number of subjects currently participating in the trial, after the completion of the Part I for dose safety assessment, about 20 patients with recurrent or refractory follicular lymphoma or marginal lymphoma will be enrolled for further evaluation. The number of patients to be enrolled in the trial has been increased from about 20 to about 40. The background knowledge of follicular lymphoma and marginal lymphoma, including morbidity, basic typing, and current clinical

Sampling in the Part II	standard treatment, has increased. In Part II, the subject will continue to collect pharmacokinetic samples. In order to increase the accuracy of the data, the collection of pharmacokinetic samples at 6 hours after dosing in Cycle 1 Day 1, and at 6 and 12 hours after dosing in Cycle 2 Day 1, has been added. Pharmacodynamic samples will not be collected in the Part II study.

Rationale: According to invetigators' suggestion, the platelet count requirement in inclusion critiria is modified.

Synopsis: 5.1 inclusion criteria:	Adequate hematological function, defined by neutrophils $\geq 1.0 \times 10^9$/L, hemoglobin≥70 g/L; and platelets $\geq 50 \times 10^9$/L if bone marrow involved; or platelets $\geq 70 \times 10^9$/L if no bone marrow involved.

Rationale: Add information on lymphocyte increase caused by BTK inhibitors, indicating that lymphocytosis is a pharmacodynamic effect of BTK inhibitors. Asymptomatic drug-related lymphocytosis are not documented and reported as adverse events.

1.1 Pharmacological action and MOA of BGB-3111 and BTK inhibitor 8.2.8.1 Asymptomatic lymphocytosis induced by study drug is not recorded and reported as an adverse event	Describe our current knowledge of reversible lymphocytosis and the observed lymphocytes increase during the treatment of BTK inhibitors, including BGB-3111, and add supportive references. Based on the clinical trial of ibrutinib, it is clearly defined that asymptomatic drug-induced lymphocytosis are not documented and reported as adverse events.

Rationale: Update the clinical data of BGB-3111, including efficacy and safety assessment.

1.4 Clinical Study of BGB-3111 1.4.2 Preliminary Efficacy of BGB-3111 1.4.3 Safety Assessment of BGB-3111	Updated clinical data from the BGB-3111 Global Phase I trial, including drug safety and efficacy analysis.

Based on the recommendations from investigators and the central ethics committee, the dose interruptions and adjustments are described in detail.

4.3 Dose Interruption and Modification 4.3.1 Dose Reductions for Hematologic Toxicity 4.3.2 Dose Reductions for Non-hematologic Toxicity	It is clearly defined that BGB-3111 treatment allows up to 28 days of continuous interruption. If a subject, after 28 consecutive days of discontinuation, is judged by the investigator that he/she can still benefit from the treatment of BGB-3111, a discussion will be conducted between the investigator and the sponsor's medical monitor to decide whether this subject could continue to receive treatment, if yes, the sponsor's medical examiner should issue a written consent form. Moreover, the dose adjustments that should be followed in the event of hematological toxicity and non-hematologic toxicity are given in more detail.

Retionale: Based on the investigator's recommendations, the requirement for bone marrow examination during the screening period was relaxed, and the bone marrow examination of the subjects with Waldenstrom Macroglobulinemia was specified in detail.

Table 3 Footnote 10 7.3.3 Bone marrow assessment	During the screening period, all subjects are required to undergo bone marrow examination (including smear and biopsy). If the bone marrow examination has been performed within 30 days before the screening period, then do not need to repeat, the test results can be used for screening period. For subjects with Waldenstrom macroglobulinemia, if bone marrow lesions are detected during the screening period, a bone marrow test should be performed every 6 months.
Rationale: The hematological examination of W1D1 is allowed to perform within 48 hours prior to administration, based on the investigator's advice.	
Table 3 Footnote 12	The hematological examination of W1D1 was allowed to be performed within 48 hours prior to administration to ensure the safety of the subject during the first administration.
Rationale: Collect additional sample to explore mechanism of drug resistance if subject experiences disease progression.	
Table 3: Table 3 Footnote 20 5.5.2 Early withdrawl 8.5 Efficacy Assessment	For subject with disease progression, blood sample or other related sample (bone marrow or lymph node) should be collected to analyze drug resistance after having obtained subject's consent.
Rationale: carambola and pomegranate juice has been added to the restricted food list.	
5.4 Restritions of Subjects	The study prohibits the consumption of any food or drink containing grapefruit juice, carambola, or pomegranate juice.
Rationale: Clarify the criteria for study completion and withdrawal from study, based on the investigator's advice.	
5.5.1 Completion of Study 5.5.3 Reasons for Withdrawal	Clarify the criteria for study completion and withdrawal from study.
Rationale: The prohibited medication is clearly defined to ensure the safety of the subjects.	
7.2 Prohibited Medication	Provide a link for complete list of QTc drugs, and clearly stipulates that during the treatment, anticoagulants or herbs should also be avoided. If there are no substitutes, please consult medical monitor and should get approval before use.
Rationale: the specific steps of PK & PD sampling and sample processing have been removed	
8.6 Pharmacokinetics 8.7 Pharmacodynamics	In order to avoid confusion, the specific steps of PK & PD sampling and sample processing have been removed. Detailed processing methods can be found in the central laboratory service manual.
Rationale: According to the CDE criteria, the association between adverse events and study drug has been modified.	

10.4 Assessment of Causality	The five-category criteria is used to assess the correlation between adverse events and study drug: certainly related, probably related, likely related, possibly unrelated, and unrelated.
Rationale: The treatment of pregnancy occurrence is described in detail.	
10.8 Pregnancies	The treatment of pregnancy occurrence is described in detail.
Rationale: Due to the limitations of the central test, the items of clinical laboratory examination have been amended.	
Appendix 1: Clinical Laboratory Test	Due to the limitations of the central test, the items of clinical laboratory examination have been amended.
Rationale: According to the latest progress, update the evaluation criteria for non-Hodgkin's lymphoma.	
Appendix 3: Efficacy Assessment Criterion	For non-Hodgkin's lymphoma, the Lugano Response criteria 2014 is used.
Rationale: According to the latest progress on Waldenstrom macroglobulinemia, a criteria of very good partial response has been updated.	
Appendix 3: Efficacy Assessment Criterion	For Waldenstrom macroglobulinemia, a criteria of very good partial response has been updated.
Rationale: A detailed specification is given for the detection of molecular markers in follicular lymphoma or marginal lymphoma subjects.	
Table 3 Footnote 19 8.8 Molecular markers	All subjects in Part II study must provide a recent study of tumor markers for molecular markers. If the subject does not have a recent sample of tumor tissue, fresh tumor biopsy must be performed during the screening period. Tumor tissue can be either formalin-fixed paraffin-embedded tumor tissue wax block or at least 10 unstained slides and sent to the central laboratory for analysis. For patients with follicular lymphoma or marginal zone lymphoma who have been enrolled (protocol 1.0), historical tumor specimens or samples should be provided after voluntary signature of new informed consent. For detailed information on tumor tissue collection, please refer to the laboratory manual.
Rationale: we found small mistakes	
overall protocol	Minor changes to grammar, format, or spelling.

SYNOPSIS

Name of Sponsor	BeiGene (Beijing) Co., Ltd
Name of Study Product	BGB-3111 capsule
Title of Study	**A phase I clinical study to investigate the safety, tolerability and pharmacokinetics / pharmacodynamics of BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma**
Protocol No.	BGB-3111-1002
Study centers	3-4 study centers
Study phase	I
Study Plan	Screening (28 days); daily treatment until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination by the sponsor, treatment (up to 3 years); safety follow-up (within 30 days of last dose); survival follow-up until study completion.

Objectives

Part I: Safety evaluation

Primary:

- To evaluate the safety and tolerability of BGB-3111 in Chinese patients with B-cell lymphoma and determine recommended phase 2 dose (RP2D).

Secondary:

- To characterize the pharmacokinetics (PK) of single- and multiple- dose of BGB-3111 orally in Chinese patients with B-cell lymphoma.
- To evaluate the inhibitory effect of BGB-3111 on BTK in peripheral blood mononuclear cells (PBMCs).

Exploratory:

- [redacted]

Part II: Dose expansion

Primary:

- To evaluate the preliminary anti-tumor activity of BGB-3111 in subjects with follicular lymphoma (FL) or marginal zone lymphoma (MZL).

Secondary:

- To further assess the safety and tolerability of BGB-3111 in patients with follicular lymphoma (FL) or marginal zone lymphoma (MZL).
- To further characterize the pharmacokinetics (PK) of single- and multiple- dose of BGB-3111 orally in Chinese patients with B-cell lymphoma.

Exploratory:

- [redacted]

Methodology:

This study is to investigate the dose safety, tolerability, pharmacokinetics and pharmacodynamics of BGB-3111 in Chinese patients with B-cell lymphoma, and to determine recommend phase II dose (RP2D), based on the multi-dose, dose escalation phase I trials which has completed in Australia and New Zealand. Based on the results that will be obtained, dose expansion studies will be performed afterwards in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL).

The study was conducted in two stages, the first stage being the safety assessment of dose, and the second stage being the dose expansion.

Part I: Safety evaluation

According to the results of preclinical toxicological trials and the results of the phase I clinical study conducted in Australia and New Zealand, two regimens of BGB-3111 320 mg daily (160 mg BID, administered in the morning and at night, or 320 mg QD) and "3+3" design is adopted for the assessment. Three eligible subjects will be enrolled for each dose regimen: first, if 1/3 (1 case) patients experience dose-limiting toxicity (DLT), another 3 subjects will be enrolled for continued observation. According to the preliminary results of the clinical study in Australia and New Zealand, two regimens of BGB-3111 320 mg dose group are both safe and tolerable. If none of the first 3 enrolled patients experiences DLT or only one patient among the 6 patients (including the supplemented 3 patients) experience DLT, then it is presumed that the dose of BGB-3111 (160 mg BID and/or 320 mg QD) is safe and tolerable. Next each dose group will recruit new patients until about 10 patients per group (including the patients enrolled previously) to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics of BGB-3111.

If more than two (inclusive) from 3 subjects or 6 subjects (including the supplemented 3 patients) experience DLT within the DLT observation window (Day 1-28), it will be concluded that the dose of BGB-3111 (160 mg BID and/or 320 mg QD) has exceeded the maximum tolerated dose (MTD) and dose should be decreaesed to 80 mg BID or 160 mg QD. Three eligible patients will be enrolled into each new dose group for re-assessment. If 80 mg BID or 160 mg QD is safe, the sponsor and investigator will analyze and discuss whether to move forward with an intermediate dose group (120 mg BID or 240 mg QD) according to the available safety data and PK data. If neither 160 mg QD and/or 80 mg BID is tolerable, the trial will be terminated.

During the trial, the sponsor, leading investigator and investigators will establish a safety monitoring committee (SMC) for ongoing safety assessment. SMC will decide the dose level and regimen for next group or if enroll more eligible patients, based on the efficacy data from the former dose level.

The toxicity observation period of BGB-3111 is 28 days and treatment observation period is from day 29 to three years. A subject will be considered end of study if he/she shows disease progression, intolerance to toxicity, death, withdrawal from the study, lost to follow-up, study termination by the sponsor, or having completed all 3 years of treatment, whichever occurs first. If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment until disease progression, intolerance, death, or withdrawal from study, under the approval by the sponsor's medical monitor. The first study analysis will be conducted after all the subjects have completed DLT assessment, and this analysis will focus on the safety and tolerability of BGB-3111. Pharmacokinetics, pharmacodynamics, will also be included in this analysis. According to the safety data of the Part I and the results of the Australian Phase I clinical trial, the dose of 160 mg BID has been selected as the RP2D. For subjects in part I, if the initial dose is 320mg QD, after the completion of DLT

assessment and with prior approval from investigator and sponsor's medical monitor, the administration regimen can be changed to 160mg BID. **Part II: Dose expansion** To further evaluate the preliminary anti-tumor effects of BGB-3111 in Chinese subjects with follicular lymphoma (FL) or marginal zone lymphoma (MZL), approximately 20 subjects with relapsed or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) will be enrolled. The recommended Phase 2 dose, 160mg BID, will be used in the Part II. Australian phase I clinical study showed good efficacy of BGB-3111 in patients with B cell malignancies, especially in subjects with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and Waldenström's macroglobulinemia. Preliminary efficacy with BGB-3111 on limited subjects with follicular lymphoma (FL) and marginal zone lymphoma (MZL) supports further investigation in approximately 20 subjects with relapsed and recurrent follicular and marginal zone lymphoma after safety evaluation in Part I. To evaluate the preliminary efficacy without harming subject's benefit, the anti-tumor activity assessment will be conducted every 12 weeks (conducted approximate every 24 weeks 1 year later) after first dose. Subjects who do not experience disease progression may continue treatment until intolerable to toxicity, death, progression of the disease, withdrawal of informed consent, or discontinuing treatment by the investigator when the risk is greater than the benefit. If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment until disease progress, intolerance, death, or withdrawal from study.	
Planned number of cases:	Approximately 40 subjects

Study Population	Inclusion criteria: • Men and women with the age of 18-75 years, voluntarily consented to the study. • Part I: Subjects with B-cell lymphoma (defined by WHO classification) refractory or relapsed following at least one line of therapy, including chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL), follicular lymphoma (FL), marginal zone lymphoma (MZL), hairy cell leukemia and non-germinal center diffuse large B cell lymphoma (DLBCL). Part II: Subjects with FL or MZL which is refractory or relapsed following at least one line of therapy. Subjects in Part II must provide recent archive tumor specimen or perform tumor biopsy. • Judged by the investigator as requiring treatment. • ECOG performance status of 0-1. • Life expectancy of at least 4 months. • Adequate hematological function, defined by neutrophils $\geq$ 1.0 x 10^9/L, hemoglobin$\geq$70 g/L; and platelets $\geq$ 50 x 10^9/L if bone marrow involved; or platelets $\geq$ 70 x 10^9/L if no bone marrow involved. • Adequate renal function, defined by creatinine clearance of $\geq$ 30 ml/min (as estimated by the Cockcroft-Gault equation or CKD-EPI equation, or as measured by nuclear medicine scan or 24 hour urine evaluation). • Adequate liver function, defined by AST and ALT $\leq$ 2.5 x ULN, and bilirubin $\leq$ 1.5 x ULN (unless documented Gilbert's syndrome). • Coagulation function: INR and APTT $\leq$ 1.5 x ULN. • Female subjects of childbearing potential and non-sterile males must practice at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, IUD or hormonal contraceptive initiated at least 3 months prior to first dose of study drug. • Male subjects must not donate sperm from start of study drug administration, until 90 days after discontinuation of treatment. **Exclusion criteria:** • With CNS involvement of the disease.

	• The pathological type of the disease has Disease transformation. • Has underdone allogeneic hematopoietic stem cell transplantation. • Has received corticosteroid anti-neoplastic treatment (>10 mg daily prednisone equivalents) within 7 days before the first dose of BGB-3111, has received radiotherapy and chemotherapy within 4 weeks before the first dose of BGB-3111 or has received treatment with monoclonal antibody within 4 weeks before the first dose of BGB-3111. • Has received BTK inhibitor treatment prior to enrollment. • Has received chemotherapy and has not yet recovered from toxicity (≤ grade 1 according to NCI-CTCAE 4.03). • Has received Chinese herbal medicine as anti-neoplastic therapy within 4 weeks before starting study treatment. • History of other malignancies within 2 years before study entry, with exception of (1) adequately cured in-situ carcinoma of cervix; (2) locally basal or squamous cell skin cancer; (3) local malignancy which has undergone radical treatment (surgery or other modality). • With uncontrolled systemic infection • Major surgery in the past 4 weeks. • With known HIV, or active hepatitis B or hepatitis C virus infection • With cardiovascular disease of New York Heart Association (NYHA) Classification ≥ 3. • QTc > 450 msecs (defined as a QTcF > 450 msecs based on the Fredericia's formula) or other significant ECG abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min). • Significant active renal, neurologic, psychiatric, hepatic or endocrinologic disease that in the investigator's opinion would adversely impact on his/her participation in the study. • Inability to comply with study procedures. • Currently taking anticoagulant drugs. • Currently taking potent CYP3A inhibitor or inducer (refer to Section 7.2 for

	details). • Had stroke or cerebral hemorrhage within 6 months before enrollment.
Dose strength	BGB-3111 20 mg and 80 mg capsules

Criteria for Evaluation:

Part I: Safety evaluation of dose

Primary Endpoints:

- Safety and tolerability of BGB-3111: The occurrence of adverse events (AEs) and serious adverse events (SAEs) of each subject will be monitored according to NCI-CTCAE4.03 grading criteria during the whole study and the safety of BGB-3111 regimen will be evaluated.

Secondary Endpoints:

- Pharmacokinetic parameters:

PK parameters for single dose: AUC_{last}、$AUC_{0-\infty}$、C_{max}、t_{max}、$t_{1/2}$、CL/F、Vd/F

PK parameters for steady status after multiple doses: AUC_{ss}、$C_{max,ss}$、$t_{max,ss}$

- The inhibitory effect of BGB-3111 on BTK activity in peripheral blood mononuclear cells will be assessed by measuring the proportion of BTK occupied in peripheral blood mononuclear cells.

Exploratory Endpoints:

[redacted]

Part II: Dose expansion

Primary Endpoints:

- Overall response rate (ORR), complete response rate (CRR), partial response rate (PRR), duration of response (DOR) and progression free survival (PFS) of BGB-3111 in subjects with FL and MZL.

Secondary Endpoints:

- Safety and tolerability of multiple dose of BGB-3111 in FL and MZL: The occurrence of adverse events (AEs) and serious adverse events (SAEs) of each subject will be monitored according to NCI-CTCAE4.03.
- Pharmacokinetic parameters:

PK parameters for single dose: AUC_{last}、$AUC_{0-\infty}$、C_{max}、t_{max}、$t_{1/2}$、CL/F、Vd/F

PK parameters for steady status after multiple doses: AUC_{ss}、$C_{max,ss}$、$t_{max,ss}$ and other applicable parameters.

Exploratory Endpoints:

- [redacted]

Statistical Methods:

Part I (Safety evaluation): The final sample size of the trial will depend on the assessed dose levels and toxicity occurrence of BGB-3111. It is expected that about 20 subjects will be enrolled in order to assess the safety and tolerability of BGB-3111 and determine RP2D.

Part II (Dose expansion): Approximately 20 subjects with relapsed or refractory FL and MZL will be enrolled to evaluate the anti-tumor activities of BGB-3111. The sample size calculation is based primarily on the accuracy level of the ORR estimate. When the sample size is 20 subjects, if the ORR is 35%, the 95% confidence interval would be (15.4%, 59.2%). The study data will be sorted and analyzed according to the statistical plan.

All subjects exposed to BGB-3111 will be included in the safety analysis population. All the subjects who have received BGB-3111 with evaluable pharmacokinetic data will be included in the pharmacokinetics analysis population and all the other evaluable parameters will be listed in the statistical report.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	**Definition**
AEs	adverse events
AUC	area under the plasma concentration-time curve
BMI	Body mass index
BTK	Bruton's tyrosine kinase
CL/F	apparent total body clearance of the drug from plasma
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CRR	complete response rate
CT	computed tomography
DBP	diastolic blood pressure
DLBCL	diffuse large B cell lymphoma
DLT	Dose limiting toxicity
eCRF	electronic case report form
EDC	Electronic data collection
EDTA	ethylene diamine tetra acetic acid
FL	follicular lymphoma
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCL	hairy cell leukemia
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ITK	interleukin-2-inducible T cell kinase
LPL	lymphoplasmacytic lymphoma
MCL	mantle cell lymphoma
MedDRA	medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	overall response rate
PBMCs	peripheral blood mononuclear cells
PPB	Plasma binding protein
RP2D	Recommended phase 2 dose
SAEs	serious adverse events
SBP	systolic blood pressure
SLL	Small lymphocytic leukemia
SMC	Safety monitor committee
SOPs	standard operating procedures
$t_{1/2}$	Terminal half time
t_{max}	Time to maximum concentration in plasma
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia

1 INTRODUCTION

1.1 Pharmacological action and MOA of BGB-3111 and BTK inhibitor

B cell receptor (BCR) signal pathway plays a critical role in the normal growth, development, differentiation and function of B cells[3]. It is known that BCR pathway is abnormally activated in various B cell malignancies such as mantel cell lymphoma (MCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma (FL), Waldenström's macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) and diffuse large B cell lymphoma (DLBCL). Bruton's tyrosine kinase (BTK) is an important signaling molecule in the BCR pathway. BTK, as a member of the non-receptor tyrosine kinase of the TEC kinase family, is expressed predominantly in the developmental stages of B lymphocytes. The activation process of the BCR pathway includes the migration of BTK to the plasma membrane, autophosphorylation of locus 223 on tyrosine, and the subsequent activation of the downstream phospholipase PLCγ2 and the release of calcium ions. These signaling events subsequently activate downstream signaling transduction pathways, including NF-κB, to promote expression of genes involved in cell proliferation and survival[4].

Studies have shown that blocking BTK signaling can inhibit the growth of B cell tumor cells, induce apoptosis and inhibit cell transfer and adhesion. Drugs targeting B-cell receptor signaling have pharmacodynamic effects that cause transient lymphocytosis, which causes BTK-mediated cell homing and adhesion to be inhibited, leading to migration of tumor cells to peripheral blood [20,21]. A reversible increase in lymphocyte count was observed at the beginning of treatment (ie, ≥50% higher than baseline, or absolute counts above 5000/mm^3). This is usually associated with alleviation of lymph node lesion, and this situation occurs to most patients with recurrent or refractory CLL/SLL during the treatment of BTK inhibitors. Some recurrent or refractory MCL patients and other B cell tumor patients showed same situation during the treatment of BTK inhibitors.

In recent years, BTK as a target for the treatment of B-cell lymphoma has made a major breakthrough. BTK inhibitor ibrutinib[5,6] has been approved by the FDA for the treatment of patients who have previously received at least one line of treatment of MCL (November 2013) and CLL (February 2014) [7-9, 12]. Recently ibrutinib was approved for the treatment of CLL with 17p deletion (July 2014) and WM (January 2015) [10,11].

BGB-3111, an independently developed BTK inhibitor, has a higher selectivity and stronger activity than ibrutinib. Biochemical and cytological studies have shown that BGB-3111 is more specific than ibrutinib for inhibition of BTK, and inhibitory activity against other kinases such as EGFR, JAK3, HER2, TEC, ITK, etc. is weaker than ibrutinib. Therefore it is expected that the toxicity of BGB-3111 in clinical trials would be lower than that of ibrutinib. In addition, due to the weak inhibition of ITK by BGB-3111, the inhibition of rituximab-induced ADCC in preclinical trials was significantly weaker than that of ibrutinib[13,14].

In addition, in vivo BTK occupancy test showed that the activity of BGB-3111 was about three times that of ibrutinib. In vivo pharmacodynamic test results also showed that BGB-3111 inhibited the growth of MCL or DLBCL subcutaneously inoculated in mice in a dose-dependent manner. At comparable doses, BGB-3111 had better tumor suppression than ibrutinib. BGB-3111 also showed good pharmacokinetic characteristics in rats and dogs with good bioavailability and could be quickly excreted from body.

According to the selectivity and efficacy shown in the preclinical study of BGB-3111, we predicted that BGB-3111 can effectively inhibit the activity of BTK kinase at a lower dose than ibrutinib in clinical practice, and because of its specificity for BTK inhibition, BGB-3111 can greatly avoid many side effects of ibrutinib arising from inhibition of other targets. More importantly, considering the ITK activity inhibition by BGB-3111 is at least 10 times weaker than that of ibrutinib, the combined effect with the clinical first-line drug rituximab may be superior to that of ibrutinib. Therefore, we expected that the efficacy of BGB-3111 monotherapy and combination therapy may be superior to that of ibrutinib in clinical trials.

**please refer to BGB-3111 investigator brochure for detailed background information.*

1.2 Pre-clinical Pharmacokinetic Study of BGB-3111

BGB-3111 showed moderate and high oral bioavailability in SD rats and Beagle dogs, with high and medium clearance rates, small volume of apparent distribution, short half-life and better linear pharmacokinetic profiles. No significant accumulation after repeated administration. The drug exposure in female rats was significantly higher than that in male rats (about twice as much), but there is no significant gender difference in the pharmacokinetic parameters for Beagle dogs.

The average plasma protein binding rates of BGB-3111 in human, cynomolgus monkey, Beagle dogs, SD rats and ICR mice were 94.2%, 93.9%, 93.3%, 96.7% and 94.9%, respectively. BGB-3111 is mainly distributed in plasma for humans and Beagle dogs, and is not distributed in a concentration-dependent manner, but is mainly distributed in plasma at low concentrations for SD rats and tends to be in blood cells at high concentrations. BGB-3111 can be quickly distributed to the body organs after oral administration, and eliminate from organs within 8 hours by a large extent.

The clearance rate of BGB-3111 in human, cynomolgus monkey, Beagle dogs, S-D rats and mouse liver microsomes was medium to high, with the clearance rate in dogs being relatively low. BGB-3111 produces a large number of metabolites in various liver microsomes and SD rats. Among the various liver microsomes, the metabolites of BGB-3111 are mainly mediated by oxidative deamination, hydroxylation, dehydration and N-desalkylation, BGB-3111 metabolism in rats is mainly mediated by cysteine binding, acetylation, glucuronidation, hydroxylation, N-desalkylation and sulfation. BYP-3111 has a certain degree of inhibition on CYP2C8, CYP2C9 and CYP2C19 with IC_{50} values of 4.03, 5.69 and 7.58 μM, respectively, which has a slight inhibitory effect on CYP2D6 and CYP3A and has no significant inhibitory effect on CYP1A2. BGB-3111 is mainly metabolized by CYP3A. BGB-3111 has no obvious effect on the activity of CYP1A2 and CYP2B6 in hepatocytes, and has a certain induction effect on CYP3A4 when the concentration is greater than or equal to 3μM.

In rats, after oral administration of BGB-3111, the excretion of parent drug via feces, urine and bile is very small. Most of ^{14}C-labeled BGB-3111 is excreted by feces, with total radioactivity recovery rate up to 98%, suggesting that in the rat BGB-3111 is mainly eliminated in body and rarely left in the body.

** Please refer to BGB-3111 investigator brochure for more information about pharmacodynamics and ADME.*

1.3 Pre-clinical Toxicological Study of BGB-3111

In vitro hERG test results showed that the inhibitory effect of BGB-3111 on hERG potassium channel was moderate, the half-inhibition concentration (IC_{50}) was 3.8 μM (positive control amitriptyline: 1.9 μM). The cardiovascular safety pharmacology telemetry test showed that 10 to 100 mg/kg of BGB-3111 had no effect on ECG, blood pressure and heart rate. BGB-3111 was administered to rats at a dose of 100 mg/kg, with no significant effect on central nervous system and respiratory function. In the single and repeated administration trials in dogs, no ECG abnormalities were observed. No abnormal clinical manifestations and/or histopathological changes associated with the cardiovascular system, central nervous system and respiratory system were found in single and repeated administration trials in rats and dogs.

The MTD (maximum tolerated dose) of rats and dogs was higher than 1000 mg/kg in a single dose acute toxicity test.

In the 14-day repeated administration exploratory study, the MTD is higher than 250 mg/kg/day for rats and higher than 100 mg/kg/day for dogs.

In the rat 28-day repeated administration study, no death associated with the test product was observed in animals. The clinical observation and clinical test changes related to the test product mainly occurred in the male and female animals of the 500 mg/kg/day group, including crusts/swelling around the nose, mouth, lips and eyelids, salivation and soft stools; WBC, NEUT and RET increased, RBC, HGB and HCT decreased; urinary occult blood/red blood cells, and positive urine protein and bilirubin. The drug exposure increased proportionally with the dose without accumulation effect, and the systemic exposure in female animals is about 1.8 to 2.9 times the same dose of male animals. Histopathological changes associated with the test product were observed in the pancreas, skin (nose and lips), spleen, prostate, large intestine and uterus. Histopathological changes in the pancreas and skin are considered toxicological; the histopathological changes of other organs or tissues are mild or mild, and are considered to be normal physiological or stress reactions and are not toxicological. Pancreatic changes occurred predominantly in male animals in all groups, with mild to moderate lesions, not dose-related, and being reversible during recovery period. Changes of skin (nose and

lips) occurred mainly in male and female animals of 500 mg/kg/day group, but not observed during the recovery period. Under the test conditions, the MTD of male and female rats was considered to be 500 mg/kg/day.

In the rat 13-week repeated administration study, the highest dose of 300 mg/kg did not result in death in rats, similar to the 28-day repeated toxicity test, including a slight decrease in K and CK. The pathological changes of pancreatic tissue are considered harmless and no new toxicity is found. Under the test conditions, the MTD of male and female rats was considered to be 300 mg/kg/day.

In the dog 28-day repeated administration study, no death was observed in all dose groups. Only animals in 100 mg/kg/day group showed a transient soft stool and vomiting during the dosing period; there was no toxicological change in body weight, food intake, hematology, blood biochemistry, and urine test. Only 30 and 100 mg/kg/day groups showed a slight increase in fibrinogen (FIB) on day 27. The drug exposure increased proportionally with the dose, and there was no significant gender difference and accumulation effect. At the end of the administration period, no significant macroscopic lesions or changes of organ weight were observed; only mild to mild spleen lymphopenia was observed in all administered animals, and no changes in hematology and organ weight were observed. This change was reversible during recovery period and was considered to have no toxicological significance. Under the test conditions, the MTD of male and female dogs was considered to be higher than 100 mg/kg/day.

In the dog 13-week repeated administration study, the highest dose was 100 mg/kg. The findings from this study were similar to the 28-day repeat administration toxicity study, and no new toxicity was found.

BGB-3111 does not cause chromosome mutations (Ames test), nor does it causes chromosome breaks (In Vitro Mammalian Cells Chromosome Aberration Test and micronucleus tests in rats).

Based on the above findings, it is considered that the clinical investigation is supported by the good safety profiles and wide safety window of BGB-3111. Drug-related changes include mild increase of WBC, NEUT and FIB; mild reduction of RET, RBC, HGB and HCT; mild reduction of K and CK; reversible harmless histopathological changes in pancreas, adrenal, lung, skin and B cell-associated lymphatic system. Histopathological changes in the pancreas were observed in rats, and the changes in male animals were more significant than in female animals with no drug relationships. The systemic exposure increased proportionally with the dose, and no significant gender differences and accumulation effects were observed.

**Please refer to investigator brochure for more toxicological information of BGB-3111.*

1.4 Clinical Study of BGB-3111

BGB-3111 is a novel, potent and highly selective BTK inhibitor developed by BeiGene, which owns the independent intellectual property rights and global patents of the product and intends to carry out clinical trials simultaneously in the world. The first-in-human (FIH) study of BGB-3111 (protocol No.: BGB-3111-AU-003) was launched in Australia in August 2014. It was an open, multi-dose, dose escalation Phase I clinical study designed to assess the safety, tolerability and pharmacokinetic characteristics of BTK inhibitor BGB -3111 in subjects with B cell lymphoma.

The safety, tolerability, and pharmacokinetics of the four doses (40 mg, 80 mg, 160 mg, and 320 mg daily) have been assessed for dose escalation of the BGB-3111 in clinical Phase I study. Of these, 40 mg, 80 mg and 160 mg were administered once daily (QD); 320 mg had two dosing regimens (320 mg QD and 160 mg BID). At present, the clinical phase II dose has been identified as 160 mg BID or 320 mg QD, and a number of further clinical trials of lymphoid tumors have been initiated. As of June 10, 2016, 125 subjects had been enrolled, and 109 of them received BGB-3111 dose of 320 mg QD or 160 mg BID; no DLT occurred. Of these, 95 subjects had received at least one assessment of drug response or early terminated treatment due to progression of the disease. The median duration of treatment was 197 days (6-633 days). The pharmacokinetics, pharmacodynamics, clinical safety, and preliminary efficacy of the drug will be described in detail below.

1.4.1 Summary of Clinical Pharmacology of BGB-3111

Based on the limited number of cases, the interim analysis of pharmacokinetic data showed that BGB-3111 was rapidly absorbed and eliminated after oral administration. The maximal plasma concentration (C_{max}) and blood exposure (AUC_{0-24h}) increased linearly in the range of 40-320 mg QD after single administration and at steady state. The half-life of

BGB-3111 is between 1.8 hours and 3.7 hours. In the 320 mg QD and 160 mg BID groups, the highest plasma concentration and blood exposure of BGB-3111 were 646 ng/mL*h and 2,704 ng/mL*h at steady state (C_{max} and AUCss), and 282 ng/mL*h and 3,006 ng/mL*h, respectively.

In the Phase I trial of BGB-3111, the drug occupancy of Bruton Tyrosine Kinase (BTK) in peripheral blood mononuclear cells (PBMCs) was examined to assess the inhibitory effect of BGB-3111 on the target. Initial analysis showed that rapid, sustained, near-to-complete inhibition was achieved even at the initial dose (40 mg) of BGB-3111. These data show that BGB-3111 is a very effective BTK inhibitor. In the dose group of 320 mg QD and 160 mg BID, the drug occupancy rate of BTK in the lymph nodes was also complete before administration on third day.

1.4.2 Preliminary Efficacy of BGB-3111

As of cut-off date (June 10, 2016), a total of 125 subjects were enrolled in the study. Except that the newly enrolled patients had not yet obtained the results of the first efficacy evaluation and 2 subjects withdrew from study due to intolerance, the remaining 95 subjects were included in the initial efficacy evaluation. In the 28 cases of treated CLL patients, the total response rate (ORR) was 93%, including 26 cases (93%) partial response (PR) and 2 cases of stable disease (SD); in the 24 cases of treated WM patients, the ORR was 93%, with a major response rate of 83%, including 8 cases (33%) very good partial response (VGPR) and 12 cases (50%) PR; in the 15 treated MCL patients, the ORR was 80%, including 3 cases (20%) complete response (CR) and 9 cases (60%) PR; in the 15 cases of treated DLBCL patients, the ORR was 25%, and the ORR reached 33% in patients of non-germinal center DLBCL. These preliminary clinical results show that BGB-3111 has a good effect in B-cell malignancies, especially in CLL, MCL, WM and DLBCL.

1.4.3 Safety Assessment of BGB-3111

As of June 10, 2016, 125 subjects had been enrolled and all subjects were included in the safety assessment. The median duration of treatment was 197 days (6-633 days), of which 17 subjects had been treated for more than 1 year and no dose-limiting toxicity (DLT) was observed, nor did it reach the maximum tolerated dose (MTD). All subjects were well tolerated with BGB-3111, and the most common adverse events (regardless of the causality) included: mild bleeding and bruising (37%), upper respiratory tract infection (25%), diarrhea 22%), cough (20%), rash (19%), lower respiratory tract infection (17%), constipation (16%), neutropenia (16%), fatigue (13%), nausea (12%) and anemia (11%). Grade ≥ 3 adverse reactions included neutropenia (16 cases), lower respiratory tract infection (10 cases), anemia (9 cases), diarrhea (2 cases) and bleeding, cough and nausea (each 1 case).

At present the trial is in progress, it will further evaluate the safety of BGB-3111.

1.5 Clinical Dose Selection of BGB-3111 in China

The selection of BGB-3111 dose in early clinical safety studies is based on the pre-clinical development guidelines for antineoplastic agents, non-clinical pharmacological data, pharmacokinetic data, and toxicological data. In rat and dog toxicology studies, the STD_{10} dose was not reached. According to the extrapolation of animal toxicological data (1/10 of the MTD of rat and dog), the starting dose of human can be up to 500mg per day.

In the clinical phase I trial in Australia and New Zealand, the dose esclation of the BGB-3111 clinical trial has been completed. The RP2D has been determined to be 160 mg twice daily or 320 mg once daily. No dose-limiting toxicity (DLT) was observed, nor did not reach the maximum tolerated dose (MTD). Up to now none subjects experienced any drug-related serious adverse effects. Of the 55 subjects currently enrolled, 5 were Asian. Based on these data, it is considered that BGB-3111 at dose of 320 mg QD or 160 mg BID would be safe and effective. The objectives of this trial is to validate the safety, tolerability and pharmacokinetic/pharmacodynamic of BGB-3111 at 320 mg QD and 160 mg BID in the Chinese population. If this dose is intolerable to the Chinese subjects, this dose will be further reduced until a safe dose is determined.

1.6 Clinical Efficacy of BTK3111 in Follicular Lymphoma and Marginal Zone Lymphoma

Follicular Lymphoma (FL) is an indolent B cell tumor originating from follicular germinal center cells. Most FL patients have been in advanced stage of disease and difficult to be cured when detected. In Western countries, FL accounts for 22% to 35% of non-Hodgkin lymphoma (NHL), and the incidence of FL in China is relatively low, accounting for 8.1% to 23.5% of NHL[16]. A high proportion of FL is transformed into diffuse large B-cell lymphoma (3%

per year)[16]. FL cells are CD10 +, CD19 +, CD22 +, CD20 + and CD5-, t (14:18) chromosome translocation and high BCL2 expression in FL are all very common. For FL patients, the median survival is about 10 years (1 - 20 years) with 5-year survival rate of 72% -77%.

Marginal Zone Lymphoma (MZL) is a B-cell lymphoma originating from the marginal zone, which is an indolent lymphoma and divided into three subtypes according to its origin, namely, extranodal MZL (also known as mucosa-associated lymphoid tissue (MALT) lymphoma), lymph node MZL and splenic marginal zone MZL. MALT lymphoma is the most common subtype, also China's most common indolent lymphoma. The prognosis of MALT lymphoma is better than lymph node MZL and spleen MZL[25].

FL is one of the malignancies very sensitive to chemotherapy and radiotherapy. For patients who need treatment, currently radiotherapy, rituximab monotherapy or combined therapy with other agents such as R-CVP and R-CHOP, has been considered as a first-line treatment. In 2010, Rituximab was approved as maintenance therapy after first-line immunochemotherapy. In 2012 Bendamustin combined with rituximab has been shown to achieve twice the progression-free survival of R-CHOP in FL patients. But FL patients are prone to recur after initial cure[15].

MALT lymphoma is the most common primary gastric MALT lymphoma. For patients at stage I and II: Hp-positive patients, anti-Hp treatment is preferred; for patients refractory to anti-Hp treatment or Hp-negative patients, local radiotherapy is preferred; for patients not suitable for radiotherapy, rituximab monotherapy could be considered; For patients at stage III and IV: patients without treatment indications may choose to keep under observation, while patients with indications can refer to the treatment principles of advanced FL, and surgical treatment is only limited to bleeding, perforation or other special circumstances. For lymph node MZL patients, the treatment principles of FL can be referred. For the spleen MZL, for patients who is asymptomatic and without progressive blood cell reduction or splenomegaly, can keep under observation. For patients with splenomegaly and positive hepatitis C virus, if there is no contraindications for hepatitis C treatment, can be given Anti-hepatitis C treatment; For patients accompanied by splenomegaly and negative hepatitis C virus, if asymptomatic, can also keep under observation; for symptomatic patients, the first choice is splenectomy or rituximab monotherapy. For patients whose disease progressed after treatment, the treatment of advanced FL can be referred[25].

BTK inhibitor ibrutinib have been approved by a number of countries, including United States, for the treatment of chronic lymphocytic leukemia, mantle cell lymphoma and Waldenstrom macroglobulinemia. Ibrutinib has also shown clinical efficacy in recurrent refractory FL and MZL subjects: Phase II clinical trials have shown an overall response rate of 30% and a tumor regression rate of 65% in relapsing refractory FL subjects; the interim progression-free survival was 9.9 months[17]. The overall response rate was 48% and tumor regression rate was 79% in the relapsed refractory MZL subjects[26]. BGB-3111, a new generation of BTK inhibitors, has a higher selectivity and stronger activity inhibition compared to ibrutinib, and is likely to inhibit tumor growth more effectively in clinical practice. In this study, approximately 20 patients with refractory follicular lymphoma or marginal lymphoma will be enrolled and the anti-tumor activity of BGB-3111 will be evaluated.

2 OBJECTIVES

2.1 Part I: Safety Evaluation of dose

2.1.1 Primary Objective

- To evaluate the safety and tolerability of BGB-3111 in Chinese patients with B-cell lymphoma and determine recommended phase 2 dose (RP2D).

2.1.2 Secondary Objective

- To characterize the pharmacokinetics (PK) of single- and multiple- dose of BGB-3111 orally in Chinese patients with B-cell lymphoma.
- To evaluate the inhibitory effect of BGB-A3111 on BTK in peripheral blood mononuclear cells (PBMCs).

2.1.3 Exploratory Objective

- [redacted]

2.2 Part II: Dose expansion

2.2.1 Primary Objective

- To evaluate the preliminary anti-tumor activity of BGB-3111 in subjects with follicular lymphoma (FL) or marginal zone lymphoma (MZL).

2.2.2 Secondary Objective

- To further assess the safety and tolerability of BGB-3111 in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL).
- To further characterize the pharmacokinetics (PK) of single- and multiple- dose of BGB-3111 orally in Chinese patients with B-cell lymphoma.

2.2.3 Exploratory Objective

- [redacted]

3 ENDPOINTS

3.1 Part I: Safety Evaluation of dose

3.1.1 Primary Endpoints:

- Safety and tolerability of BGB-3111: The occurrence of adverse events (AEs) and serious adverse events (SAEs) of each subject will be monitored according to NCI-CTCAE4.03 grading criteria during the whole study and the safety of BGB-3111 regimen will be evaluated.

3.1.2 Secondary Endpoints:

- Pharmacokinetic parameters:

PK parameters for single dose: AUC_{last}、$AUC_{0-\infty}$、C_{max}、t_{max}、$t_{1/2}$、CL/F、V_d/F

PK parameters for steady status after multiple doses: AUC_{ss}、$C_{max,ss}$、$t_{max,ss}$

- The inhibitory effect of BGB-3111 on BTK activity in peripheral blood mononuclear cells will be assessed by measuring the proportion of BTK occupied in peripheral blood mononuclear cells.

3.1.3 Exploratory Endpoints:

- [redacted]

3.2 Part II: Dose Expansion

3.2.1 Primary Endpoints:

- Overall response rate (ORR), complete response rate (CRR), partial response rate (PRR), duration of response (DOR) and progression free survival (PFS) of BGB-3111 in subjects with follicular lymphoma (FL) and marginal zone lymphoma (MZL).

3.2.2 Secondary Endpoints:

- Safety and tolerability of BGB-3111 in FL and MZL: The occurrence of adverse events (AEs) and serious adverse events (SAEs) of each subject will be monitored according to NCI-CTCAE4.03.
- Pharmacokinetic parameters:

  PK parameters for single dose: AUC_{last}、$AUC_{0-\infty}$、C_{max}、t_{max}、$t_{1/2}$、CL/F、Vd/F

  PK parameters for steady status after multiple doses: AUC_{ss}、$C_{max,ss}$、$t_{max,ss}$ and other applicable parameters.

3.2.3 Exploratory Endpoints:

- [redacted]

4 STUDY DESIGN

4.1 Overall Design

This study is to investigate the dose safety, tolerability, pharmacokinetics and pharmacodynamics of BGB-3111 in Chinese patients with B-cell lymphoma, and to determine the RP2D, based on the multi-dose, dose escalation phase I trials which has completed in Australia and New Zealand. Based on the results that will be obtained, dose expansion studies will be performed afterwards in patients with indolent lymphoma, including follicular lymphoma (FL) and marginal zone lymphoma (MZL).

The study was conducted in two stages, the first stage being the safety assessment of dose, and the second stage being the dose expansion.

Part I: Safety evaluation

According to the results of preclinical toxicological trials and the results of the phase I clinical study conducted in Australia and New Zealand, two regimens of BGB-3111 320 mg daily (160 mg BID, administered in the morning and at night, or 320 mg QD) and "3+3" design is adopted for the assessment. Three eligible subjects will be enrolled for each dose regimen: first, if 1/3 (1 case) patients experience dose-limiting toxicity (DLT), another 3 subjects will be enrolled for continued observation. According to the preliminary results of the clinical study in Australia and New Zealand, two regimens of BGB-3111 320 mg dose group are both safe and tolerable. If none of the first 3 enrolled patients experiences DLT or only one patient among the 6 patients (including the supplemented 3 patients) experience DLT, then it is presumed that the dose of BGB-3111 (160 mg BID and/or 320 mg QD) is safe and tolerable. Next each dose group will recruit new patients until about 10 patients per group (including the patients enrolled previously) to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics of BGB-3111.

If more than two (inclusive) from 3 subjects or 6 subjects (including the supplemented 3 patients) experience DLT within the DLT observation window (Day 1-28), it will be concluded that the dose of BGB-3111 (160 mg BID and/or 320 mg QD) has exceeded the maximum tolerated dose (MTD) and dose should be tapered down to 80 mg BID or 160 mg QD. Three eligible patients will be enrolled into each new dose group for re-assessment. If 80 mg BID or 160 mg QD is safe, the sponsor and investigator will analyze and discuss whether to move forward with an intermediate dose group (120 mg BID or 240 mg QD) according to the available safety data and PK data. If neither 160 mg QD and/or 80 mg BID is tolerable, the trial will be terminated.

During the trial, the sponsor, leading investigator and investigators will establish a safety monitoring committee (SMC) for ongoing safety assessment. SMC will decide the dose level and regimen for next group or if enroll more eligible patients or add unscheduled dose(s) into study, based on the efficacy data from the former dose level, and decide the RP2D.

For the BID group, the subject will receive only the morning dose (half of the daily dose) on Day 1 of the study for the 24-hour PK evaluation. From the next day, administration will be shifted to once in the morning and evening respectively with an interval of 12 hours ± 2 hours. It is strongly recommended to take the medicine at the same time every day.

The toxicity observation period of BGB-3111 is 28 days (Day 1-28) and treatment observation period is from day 29 to three years. A subject will be considered end of study if he/she shows disease progression, intolerance to toxicity, death, withdrawal from the study, lost to follow-up, study termination by the sponsor, or having completed all 3 years of treatment, whichever occurs first. If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment until disease

progression, intolerance, death, or withdrawal from study, under the approval by the sponsor's medical monitor.

The first subject (outpost subjects) in each dose group will be hospitalized and keep under observation for 24 hours after receiving the first single dose administration and will be not allowed to continue enrollment within this 24-hour hospitalization, so as to avoid the occurrence of accidence or acute toxicity. According to the safety data of the Part I and the results of the global Phase I clinical trial, 160 mg of BID has been identified as the RP2D.

If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment until disease progress, intolerance, death, or withdrawal from study, under the approval by the sponsor's medical monitor.

Part II: Dose expansion

To further evaluate the preliminary anti-tumor effects of BGB-3111 in Chinese subjects with follicular lymphoma (FL) or marginal zone lymphoma (MZL), approximately 20 subjects with relapsed or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) will be enrolled. The RP2D determined in Part I, i.e. 160mg BID, will be used in the Part II.

To evaluate the preliminary efficacy without harming subject's benefit, the anti-tumor activity assessment will be conducted every 12 weeks (conducted approximate every 24 weeks 1 year later) after first dose. Subjects who do not experience disease progression may continue treatment until intolerable to toxicity, death, progression of the disease, withdrawal of informed consent, or discontinuing treatment by the investigator when the risk is greater than the benefit. If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment until disease progression, intolerance, death, or withdrawal from study.

4.2 Dose Limiting Toxicity (DLT)

The DLT evaluation period is defined as from the first use of BGB-3111 to the day 28 after administration.

All toxicity and adverse events will be assessed according to the NCI CTCAE V4.03[2] grading criteria, and the following events will be defined as DLT:

Dose Restriction Toxicity (DLT) refers to a drug-related toxicity or adverse event that occurs during the treatment of the DLT evaluation period (days 1-28) and meets the following criteria and does not include an event that is not associated with BGB-3111: Disease progression, underlying disease, concurrent disease or concomitant treatment).

- Grade 4 neutropenia sustained for more than 7 days (in the condition of receiving growth factors) or ≥ grade 3 febrile neutropenia (≥38.3°C or continuous fever of ≥38.0°C lasting for more than 1 hour).
- Grade 4 thrombocytopenia or ≥ grade 3 thrombocytopenia associated with bleeding.
- Other grade ≥2 non-hematological toxicity which need dose adjustment of BGB-3111 or administration delay over 1 week.
- Other grade ≥3 drug-related non-hematological toxicity (excluding of asymptomatic abnormal laboratory results with no clinical significance and non-hematological toxicity which has recovered to grade≤2 within 7 days).
- Any degree of toxicity requiring withdrawal from study as per investigator or sponsor's judgement.

When DLT occurs, blood sample (4mL) should be collected as soon as possible to analyze plasma concentration of BGB-3111. If DLT toxicity has recovered to Grade ≤ 1 within 14 days after DLT has been treated and treatment interruption or delay is ≤ 28 days, the BGB-3111 treatment can be resumed at 50% of dose. When other drug-related serious adverse reactions occur, if the investigator and the sponsor's medical monitor consider it necessary,

blood sample (4 mL) should be collected as soon as possible to analyze the mechanism of the event.

If a subject discontinues treatment in the evaluation window of the DLT not due to drug-related toxicity and has received less than 75% of the defined dose, the subject will be excluded from the DLT evaluation and should be replaced by a new subject.

4.3 Dose Interruption and Modification

In the event of hematologic toxicity (4.3.1) or non-hematologic toxicity (4.3.2), the dose reduction of BGB-3111 as specified in Table 2 should be followed.

Table 2 Dose Reduction of BGB-3111 for toxicity

Dose Level	BGB-3111 Daily Dose	
0 = starting dose	320 mg QD	160 mg BID
-1 dose level	160 mg QD	80 mg BID
-2 dose level	80 mg QD	80 mg QD

BID= twice daily, QD=once daily

BGB-3111 treatment allows up to 28 days of continuous interruption. If a subject, after 28 consecutive days of discontinuation, is judged by the investigator that he/she can still benefit from the treatment of BGB-3111, the investigator and the sponsor's medical monitor should discuss and decide whether to continue treatment; if yes, a written consent shall be issued by the sponsor's medical monitor.

4.3.1 Dose Reductions for Hematologic Toxicity

If the subject shows the following symptoms, the treatment of BGB-3111 will be discontinued and the subject will be treated according to the clinical situation.

- Grade 4 neutropenia (sustained > 7 days, discontinue treatment if clinically necessary)
- Grade 4 thrombocytopenia (sustained > 7 days, discontinue treatment if clinically necessary)
- Grade≥ 3 febrile neutropenia
- Grade≥ 3 thrombocytopenia with bleeding

When the toxicity has recovered to Grade 1 or baseline, BGB-3111 treatment can be resumed with prior dose. If the same toxicity recurs, the treatment should be resumed at 50% dose level when the toxicity has recovered to Grade ≤1 or baseline. The dose is allowed to be reduced up to twice.

If a subject experiences Grade≥3 thrombocytopenia with significant bleeding symptoms requiring treatment, the subject needs to discontinue treatment and withdraw from study.

The study drug-induced lymphocytosis is an expected event and may occur frequently. In this study, subjects with asymptomatic, study drug-induced lymphocytosis, including the triggered leukocytosis, could continue to receive study drug.

4.3.2 Dose Reductions for Non-hematologic Toxicity

The treatment of BGB-3111 will be discontinued if a subject experiences a Grade ≥3 drug-related non-hematologic toxicity (except arrhythmia or oral medication controllable hypertension). The BGB-3111 treatment can be resumed when the toxicity has recovered to ≤ Grade 1, but it should start from -1 dose level (i.e. reduce by 50%). If the same toxicity recurs at Grade ≥3, it is necessary to discontinue BGB-3111 treatment until it has recovered to ≤ Grade 1, then

start from -2 dose level. If the same toxicity recurs even at Grade ≥3 at -2 dose level, this subject should discontinue treatment permanently and withdraw from study. If a subject experienes managable arrhythmia, the BGB-3111 treatment may be continued as original dose or at a dose of 50% when the toxicity has recovered to ≤ Grade 1, depending on the decision of the investigator.

Other special circumstances shall be discussed and decided between investigator and medical monitor.

For study assessments schedule, and pharmacokinetic and pharmacodynamic sampling, please refer to stable 3, table 4, and table 5.

Table 3 Study Assessments and Procedures Schedule

	Screening [1]	Treatment Period [2]								End of Study		
		Weeks 1 to 4 (DLT period)				Weeks 5 to 8		Weeks 9 to 53	Wk53+	EOT[3]	Safety follow-up[3]	Survival follow-up
Days	-28 to -1	W1 D1	W1 D2	W2 D1	W3 D1	W5 D1	W7 D1	Every 4 weeks	Every 8 weeks	Within 7 days after stopping treatment	30 days after last dose	
Window (days)				± 1	± 1	± 3	± 3	± 3	± 7		± 7	
Informed consent [4]	x											
Inclusion/exclusion criteria	x											
Demographic data	x											
Medical history/baseline conditions	x											
Vital signs	x	x		x	x	x	x	x	x	x	x	
Weight (& Height at screening)	x	x				x				x	x	
B-symptoms [5]	x	x				x				x		
Complete physical examination [6]	x											
Targeted physical examination [6]		x		x	x	x	x	x	x	x		
ECOG performance status	x	x				x				x	x	
Echocardiogram	x											
12-lead ECG [7]	x	x	x	x		x	x	x	x	x		
Drug administration [8]		x once or twice daily										
Concomitant medications	x	x		x	x	x	x	x	x	x	x	
Adverse events/serious adverse events	x	x	x	x	x	x	x	x	x	x	x	
Tumour assessment by CT/PET-CT scan [9]	x	Every 12 weeks (end of week 12, 24, 36 and 48), then every 24 weeks										
Bone marrow aspiration or biopsy [10]	x	x[10]										
Laboratory Test												
Hematology [11]	x	x		x	x	x	x	x	x	x		
Clinical chemistry [12]	x	x		x	x	x	x	x	x	x		
Coagulation	x	x				x		x	x			
IgA, IgG, IgM level and immunofixation electrophoresis [13]	x					x		x	x	x		
Pregnancy test [14]	x	x				x		x	x			
Viral serologies [15]	x											
Routine urine test [16]	x	x		x	x	x	x	x	x	x		
Pharmacokinetic blood sampling [17]		x	x	x		x		x				

	Screening [1]	Treatment Period [2]								End of Study		
		Weeks 1 to 4 (DLT period)				Weeks 5 to 8		Weeks 9 to 53	Wk53+	EOT[3]	Safety follow-up[3]	Survival follow-up
Days	-28 to -1	W1 D1	W1 D2	W2 D1	W3 D1	W5 D1	W7 D1	Every 4 weeks	Every 8 weeks	Within 7 days after stopping treatment	30 days after last dose	
Window (days)				± 1	± 1	± 3	± 3	± 3	± 7		± 7	
Pharmacodynamic blood sampling [18]		x	x	x								
Tumor tissue sampling [19]	x											
Anti-tumor therapy after treatment											x	x
Survival follow-up[20]												x

Abbreviations: The subjects' physical status scale was developed by the Eastern Cooperative Oncology Group (ECOG); x: to be performed

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

1. Screening period is from Day -28 to -1, during which all criterias should be strictly assessed.
2. The treatment observation period lasts for 28 days (DLT window), and the subsequent observation period is from Day 29 to having finished continuous treatment for about 3 years. During the treatment, the treatment may be discontinued when disease progress, intoleratable to toxicity, death, whithdrawal from study, termination by the sponsor or having completed all three years of treatment. If a subject continues to benefit from treatment, only if approved by the sponsor's medical monitor, this subject can be transferred to extension study for continuous treatment until disease progress, intolerance, death, withdrawal from study, or discontinuing treamtment by investigator. After 9 weeks, clinical visit should be conducted every four weeks (Day 1 ±3 of Week 9, so does at Week 13, and so on. The last two visits will be performed at Week 45 and Week 49) and shift to every 8 weeks (Week 57, Week 65 and Week 73 etc.).
3. If possible, subjects will conduct clinical visit within 7 days after the treatment is discontinued. The safety follow-up should be conducted within 30 (± 7) days after the last dose of BGB-3111 or just before the new anti-tumor therapy is initiated to collect AEs/SAEs that occurred after the treatment. Investigator or other designated personnel should also collect the information about new anti-tumor therapy. If the interval between EOT visit and satefy follow-up visit is less then 1 week, the EOT visit can be delayed to be together with the safety follow-up visit.
4. Written informed consent form(s) must be signed by the patient before any study-specific procedures are performed.
5. Unexplained weight loss > 10% over previous 6 months, fever (>38°C), and night sweat.
6. Complete physical exam includes all systems of body, while targeted physical exam is only limited to systems (e.g. cardiovascular, respiratory, lymph nodes, liver, and spleen) associated with clinical signs/symptoms.
7. Conduct a 12-lead electrocardiogram during the screening period (in triplicate) and final follow-up visit for treatment completion/early termination. For the time points of pharmacokinetic sampling and electrocardiogram examination, please refer to Table 4 and Table 5. Subjects should be in the lateral position or supine position for ECG examination. Note: not all ECG assessments should be performed in accordance with Table 3.
8. BGB-3111 should be administered once daily or twice daily until end of the treatment. If the regimen is twice daily, it is administered only once (in the morning) at W1D1 and twice daily starts from W1D2 (in the morning and at night respectively).
9. Tumor evaluation should be performed within 7 days after week 12, 24, 36 and 48 of the treatment and thereafter within 2 weeks of every 24 weeks ends (for hair follicle leukemia subjects, it should be performed within 7 days of the ends of week 12, 24, 36, 48 of treatment, then follows local practice after one year). Contrast-enhanced CT scans including neck, chest, abdomen, and pelvis are used for tumor assessment. Using CT as a diagnostic standard in PET/CT is acceptable as long as the long and short axises of lymph nodes, liver, and spleen is provided. Investigators may

determine whether MRI is to be used instead of CT, or whether PET-CT is to be performed during screening. For subjects with positive PET-CT during screening, it is required to conduct re-examination when confirming CR. For the early termination visit, CT scan is required if the previous scan was performed more than 3 months ago.

10. All subjects need to perform bone marrow examination (including smear and biopsy) during the screening period. If bone marrow examination was performed 30 days before screening, it does not need to repeat and the results could be used for screening. For subjects with Waldenstrom's macroglobulinemia, a bone marrow test should be performed every 24 weeks. Subjects who have been diagnosed with bone marrow lesions at the time of enrollment may need to undergo further bone marrow aspiration and biopsy to confirm CR if this case is judged to be possible CR by physical examination or CT scan.
11. Hematology includes RBC count, hemoglobin, hematocrit, reticulocyte count (optional), 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 (platelet count $< 50{,}000/mm^3$), or Grade ≥ 3 toxicity, the test may need to repeat at any time based on doctor's judgement, until toxicity resolves to Grade ≤ 2. The hematological test of W1D1 is allowed to take place within 48 hours prior to administration.
12. Clinical chemistry includes potassium, sodium, chloride, calcium, phosphorus, magnesium, CO_2, total protein(TP), albumin(ALB), blood glucose, urea nitrogen, creatinine, alkaline phosphatase(ALP), lactic dehydrogenase(LDH), total bilirubin(BIL), direct bilirubin, aspartate aminotransferase(AST), alanine aminotransferase(ALT) and uric acid. In the event of Grade ≥3 clinical chemistry toxicity, the test may need to repeat at any time based on doctor's judgement, until toxicity resolves to Grade ≤ 2. The clinical chemistry test of W1D1 is allowed to take place within 48 hours prior to administration.
13. All patients with Waldenstrom macroglobulinemia will undergo a first immunofixation electrophoresis test at the time of screening. If monoclonal proteins are found, this test need to repeat at follow-up.
14. 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.
15. The virus serology includes hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc); hepatitis C antibody and AIDS virus.
16. If urine protein ≥2+ in urinal microscopic examination, the 24-h urine sample should be collected to test the 24h total urine protein (Refer to Section 8.2.1 assessment at laboratory of study center for details).
17. The details of the time points of the continuous pharmacokinetics sampling detail in Table 4 and Table 5.
18. The pharmacodynamics blood sampling is only for subjects of Part I, and the time points for collection detail in Table 4.
19. Patients with diffuse large B cell lymphoma must provide archive tumor tissues or fresh tumor biopsy to confirm DLBCL subtype. Subjects with FL or MZL must provide recent archive tissue for the biomarker analysis. If no tumor specimens are available, needle-biopsy of lymph nodes which is symptomatic during the screening period and can be sampled, may be considered. For subjects with FL or MZL who have been enrolled under the protocol version 1.0, the archive tissue or fresh tumor biopsy should be collected after the new ICF is signed.
20. For subject with disease progression, blood sample or other related sample (bone marrow or lymph node) should be collected to analyze drug resistance after having obtained subject's consent.
21. After the final visit, the survival follow-up will be conducted every 3 months until withdrawal of consent, loss to follow-up, death, or the cut-off date of final data analysis. Investigators or their authorized personnel will also continue to collect information on the use of new anti-cancer therapies given after the last dose of the study drug.

Table 4 Pharmacokinetic and Pharmacodynamic Sampling in the Part I.

Procedure	**W1 D1**								**W1 D2**	**W2 D1**							**W5 D1**	**W9 D1**
Hours	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**8**	**12**	**24 1**	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**8**	**Pre-dose**	**Pre-dose**
ECG examination	X[5]		X[2]	X[3]	X[3]	X[3]	X[4]	X[4]	X[5]	X[5]		X[2]	X[3]	X[3]	X[3]	X[3]	X[5]	X[5]
Vital signs	X[5]	X[2]	X[2]	X[3]	X[3]	X[3]	X[4]	X[4]	X[5]	X[5]	X[2]	X[2]	X[3]	X[3]	X[3]	X[3]	X[5]	X[5]
Pharmacokinetic blood sampling	X[5]	X[2]	X[2]	X[3]	X[3]	X[3]	X[4]	X[4]	X[5]	X[5]	X[2]	X[2]	X[3]	X[3]	X[3]	X[3]	X[5]	X[5]
Pharmacodynamic blood sampling	X[5]					X[3]			X[5]	X[5]								

Note: It is important that the pharmacokinetics (PK) and pharmacodynamics (PD) sampling times should be consistent with their scheduled time. To achieve this, other assessment items at the same time are allowed to be advanced or delayed so that there is sufficient time to complete the PK / PD blood sampling. Thus, an operation order as follows is recommended: 1) ECG (in triplicate at each PK blood pointsexcept 0.5 hours)), 2) measurement of vital signs, 3) PK / PD blood sampling (at the precise scheduled time as far as possible), 4) other tests / assessments.

1. On W1D2, before the morning dose.
2. The window period is ±10 minutes.
3. The window period is ±20 minutes.
4. The window period is ±30 minutes.
5. Within 2 hours prior to dosing.

Table 5 Pharmacokinetic Sampling in the Part II.

Procedure	**W1 D1**									**W1 / D2**	**W2 D1**								**W5 D1**	**W9 D1**
Hours	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24 [1]**	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**Pre- dose**	**Pre-dose**
ECG examination	X [5]			X [3]							X [5]			X [3]						X [5]	X [5]
Vital signs	X [5]	X [2]	X [2]	X [3]	X [3]	X [3]	X [4]	X [4]	X [4]	X [5]	X [5]	X [2]	X [2]	X [3]	X [3]	X [3]	X [3]	X [4]	X [4]	X [5]	X [5]
Pharmacokinetic blood sampling	X [5]	X [2]	X [2]	X [3]	X [3]	X [3]	X [4]	X [4]	X [4]	X [5]	X [5]	X [2]	X [2]	X [3]	X [3]	X [3]	X [3]	X [4]	X [4]	X [5]	X [5]

Note: It is important that the pharmacokinetics (PK) sampling times should be consistent with their scheduled time. To achieve this, other assessment items at the same time are allowed to be advanced or delayed so that there is sufficient time to complete the PK blood sampling. Thus, an operation order as follows is recommended: 1) ECG (in triplicate at each PK blood points,), 2) measurement of vital signs, 3) PK blood sampling (at the precise scheduled time as far as possible), 4) other tests / assessments.

1. On W1D2, before the morning dose.
2. The window period is ±10 minutes.
3. The window period is ±20 minutes.
4. The window period is ±30 minutes.
5. Within 2 hours prior to dosing.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects are eligible for inclusion in the study if they meet all of the following criteria:

- Men and women with the age of 18-75 years, voluntarily consented to the study.
- Part I: Subjects with B-cell lymphoma (defined by WHO classification) refractory or relapsed following at least one line of therapy, including chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL), follicular lymphoma (FL), marginal zone lymphoma (MZL), hairy cell leukemia and non-germinal center diffuse large B cell lymphoma (DLBCL). Part II: Subjects with FL or MZL which is refractory or relapsed following at least one line of therapy. Subjects in Part II must provide recent archive tumor specimen or perform tumor biopsy.
- Judged by the investigator as requiring treatment.
- ECOG performance status of 0-1.
- Life expectancy of at least 4 months.
- Adequate hematological function, defined by neutrophils $\geq 1.0 \times 10^9$/L, hemoglobin≥70 g/L and platelets $\geq 50 \times 10^9$/L if bone marrow involved; or platelets $\geq 70 \times 10^9$/L if no bone marrow involved..
- Adequate renal function, defined by creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or CKD-EPI equation, or as measured by nuclear medicine scan or 24 hour urine evaluation).
- Adequate liver function, defined by AST and ALT ≤ 2.5 x ULN, and bilirubin ≤ 1.5 x ULN (unless documented Gilbert's syndrome).
- Coagulation function: INR and APTT ≤ 1.5 x ULN.
- Female subjects of childbearing potential and non-sterile males must practice at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, IUD or hormonal contraceptive initiated at least 3 months prior to first dose of study drug.
- Male subjects must not donate sperm from start of study drug administration, until 90 days after discontinuation of treatment.

5.2 Exclusion Criteria

Subjects are to be excluded from the study if they meet any of the following criteria:

- With CNS involvement of the disease.
- The pathological type of the disease has Disease transformation.

- Has underdone allogeneic hematopoietic stem cell transplantation.
- Has received corticosteroid anti-neoplastic treatment (>10 mg daily prednisone equivalents) within 7 days before the first dose of BGB-3111, has received radiotherapy and chemotherapy within 4 weeks before the first dose of BGB-3111 or has received treatment with monoclonal antibody within 4 weeks before the first dose of BGB-3111.
- Has received BTK inhibitor treatment prior to enrollment.
- Has received chemotherapy and has not yet recovered from toxicity (≤ grade 1 according to NCI-CTCAE 4.03).
- Has received Chinese herbal medicine as anti-neoplastic therapy within 4 weeks before starting study treatment.
- History of other malignancies within 2 years before study entry, with exception of (1) adequately cured in-situ carcinoma of cervix; (2) locally basal or squamous cell skin cancer; (3) local malignancy which has undergone radical treatment (surgery or other modality).
- With uncontrolled systemic infection.
- Major surgery in the past 4 weeks.
- With known HIV, or active hepatitis B or hepatitis C virus infection.
- With cardiovascular disease of New York Heart Association (NYHA) Classification ≥ 3.
- QTc > 450 msecs (defined as a QTcF > 450 msecs based on the Fredericia's formula) or other significant ECG abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).
- Significant active renal, neurologic, psychiatric, hepatic or endocrinologic disease that in the investigator's opinion would adversely impact on his/her participation in the study.
- Inability to comply with study procedures.
- Currently taking anticoagulant drugs.
- Currently taking potent CYP3A inhibitor or inducer (refer to Section 7.2 for details).
- Had stroke or cerebral hemorrhage within 6 months before enrollment.

5.3 Other Consideration for eligibility

Any potential or safety impact on the subject needs to be adequately addressed, and the investigator must refer to the ICF for detailed information, precautions, warnings, contraindications, adverse events, and important data from this study or other studies which used this product.

5.4 Restrictions of Subjects

The following restrictions may have an effect on the results of this study:

- From the screening group to the end of the study, the subject should inform the investigator as soon as possible if using any drug.

- In the course of the study, subjects should be fasted except drinking water in 2 hours before administration and 1 hour after administration; the study prohibits the consumption of any grapefruit juice, carambola, or pomegranate juice of food or drink, other diet is not limited.

5.5 Completion of Study and and Early Withdrawal

5.5.1 Completion of Study

Subjects who have completed the pharmacokinetic sample collection (including data for Day 1 Week 2) and did not withdraw from study before completion of the DLT evaluation period (from BGB-3111 first administration to 28 days) will be deemed to complete the study. The Subjects will continue to receive study drug until completion of the three-year treatment period, or until disease progression, intolerable toxicity or death, withdrawal of informed consent, loss of follow-up or termination of trial by sponsor, whichever occurs first. If a subject still have clinical benefits after completing the three-year treatment, he/she can be transferred to the extension study under approval by the medical monitor. The need to stop the study treatment will not cause the subject to withdraw from the study automatically. A subject should discontinue study treatment if any of the following occurs:

- Significant disease progression or relapse
- Unacceptable toxicity
- Pregnancy
- Subject refuse further treatment
- Major protocol deviation determined by primary investigator or sponsor
- For safety reasons (such as adverse events), the investigator believe that discontinuing treatment is in line with the best benefit of the subject

The reasons for treatment discontinuation will be recorded in source document and CRF. Investigator should try to complete safety follow up visit at 30 days after the last dose.

5.5.2 Early Withdrawal

Subjects may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Investigator should evaluate following items within 7 days of study termination: physical examination, vital signs, 12 lead ECG, ECOG performance, B-symptoms, ECG, laboratory test (complete blood count, blood biochemistry, urinalysis, and serum immunoglobulin), concomitant medication and AE assessment, which will be recorded as basic assessment before withdrawal. Furthermore, if possible, safety follow up should be conducted within 30±7 days after the last dose and thereafter every 3 months for survival follow up.

Subjects who withdraw from study due to adverse event (for definition refer to section 10.1) at any time must be treated according to procedures in section 10.6.

If a DLT occurs, 4 mL of blood sample should be collected as soon as possible to analyze the plasma concentration of BGB-3111. If drug related SAE occurs, 4mL of blood sample should be collected as soon as possible if regarded as needed by investigator and sponsor's medical monitor. For subject with disease progression, blood sample or other related sample (bone marrow or lymph node) should be collected to analyze drug resistance after having obtained subject's consent.

A subject who withdraw from the study for any reason or withdraw the informed consent form will not be replaced unless he/she is withdrawn due to DLT(s), in which case the sponsor and the SMC may consider replacement.

5.5.3 Reasons for Withdrawal

Subjects will be withdrawn from study for any of the following:

- Subject withdraw consent

- Study of BGB-3111 is terminated by sponsor
- Lost to follow-up

If subject lost to follow-up, investigator should try best to contact subject and confirm reasons for discontinuation /withdrawal and document the reasons in source document and CRF before withdrawal.

6 STUDY TREATMENT

6.1 Study Drug

According to different doses received by subjects, BGB-3111 formulation is 20 mg and 80 mg capsules (20 mg is blue opaque 3# capsules, 80 mg is white opaque 0# capsule).

6.2 Dosage and Administration

The initial dose of BGB-3111 administration is 320 mg daily (320 mg QD or 160 mg BID). For the BID regimen, only 160 mg morning dose will be administered on day 1, from day 2 to the end of treatment, twice daily (160 mg BID) (once in the morning, once in the evening, an interval of 12 ± 2 hours is highly recommended) will be administered. Swallow the capsules with a glass of boiled water. If the evening dose is not taken within 12 ± 2 hours of scheduled time, the actual medication time needs to be recorded on the patient log.

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.

Subjects will continuous take study drug until intolerance to toxicity, disease progression, subject or investigator decides to withdraw from study. If the treatment has been interrupted for more than 4 weeks, the subject may take short-term prohibited drug specified in the protocol under approval by the doctor and dafety monitor.

Subjects cannot take food within 2 hours before and 1 hour after drug administration.

The DLT observation period of BGB-3111 is 28 days (Day 1-28) and subsequent treatment period is from day 29 to having been in continuous treatment for 3 yeas. The treatment may be discontinued when disease progression, intolerable to toxicity, death, withdrawal from the study, lost to follow-up, study termination by the sponsor, or having completed all 3 years of treatment, whichever occurs first. If a subject is judged to still have clinical benefit by the investigator at the end of 3-year treatment, he/she may be transferred to the extension study to continue BGB-3111 treatment under the approval by the sponsor's medical monitor.

6.3 Subject Numbering

Subjects can only 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. If a subject is replaced, new enrolled subject will be assigned next effective subject number.

6.4 Packaging and Labelling

The capsule supplies of BGB-3111 will be provided in a child-resistant high density polyethylene (HDPE) bottle with induction seal and bottle label. The label will include: drug quantity, protocol number, batch number, directions for usage, storage conditions, expiry date, space to enter the subject number and abbreviation of name. The contents of the label will be in accordance with all applicable local regulatory requirements.

6.5 Drug 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 in this protocol. Only enrolled subjects can receive study drug, in accordance with all applicable regulatory requirements. Only authorized study personnel can

supply or manage study drug. All study drugs must be stored in a secure area with access limited to the investigator and authorized study personnel, and stored under 15°C -30°C or under conditions required by latest investigator brochure.

6.6 Responsibility of Study Drug Management

Investigator is responsible for usage, dispensation, and recording of the study drug. According to the existing regulatory requirements, investigators or designated personnel of the study center shall record the acceptance, distribution, usage and recycling of the study drug throughout the course of the study.

After completion of the study, all unused BGB-3111 will be inventoried and packaged for return shipment by the hospital pharmacist. The inventoried supplies will be returned to the sponsor or destroyed on site, after having received written approval from sponsor.

6.7 Compliance Assessment

All subjects will need to answer questions about compliance before being recruited across all study centers.

In the course of study, investigators will dispense dosage according to dose group and record actual dose exactly. The actual dose should be consistent with dose in protocol. Compliance will be determined according to number of study drug dispensed to and return by subjects in every treatment cycle and at the time of study discontinuation.

6.8 Handling of Study Overdose

If the subject is suspected of overdose, routine supportive care should be given, and subsequent treatment will be determined by investigator after discussion with medical monitor, and any adverse events due to overdose will be reported to the medical monitor.

6.9 Occupational Risk

The use and management of study drug under normal conditions does not pose a significant occupational safety risk to study center personnel.

7 CONCOMITANT MEDICATIN AND PROHIBITED MEDICATION

7.1 Concomitant Medication

All concomitant medication will be recorded in source document and CRF during study, including its indication, dosage and dates of administration.

7.2 Prohibited Medication

Subject cannot receive other anti-tumor treatment during study, including but not limitedto chemotherapy, biotherapy, hormotherapy and other study drug. Diphosphonate could be used if it has been at stable dose 3 month before enrollment. Corticosteroid for not more than 2 weeks is permitted if it is used in other indications (not cancer). If there are no other alternative, the treatment should be decided by investigator after discusstion with medical monitor and a written approval should be issued firstly by sponsor's medical monitor.

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. For a complete list please refer to http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm and Appedix 6. If the drug has to be used in special circumstances, the treatment should be decided by investigator after discussion with medical monitor, and a written approval should be issued firstly by sponsor's medical monitor.

Anticoagulation drug and Chinese herbal medication should be avoided during study. If no other alternatives, the treatment should be decided by investigator after discussion with medical monitor, and a written approval should be issued firstly by sponsor's medical monitor.

Results of in vitro study indicate BGB-3111 is not a strong inhibitor of human CYP isoenzyme. However CYP3A involves main metabolic route of BGB-3111. Table 6 lists prohibited medication in this study (strong inhibitor and inducer of CYP3A), for a more completed list please refer to: http://medicine.iupui.edu/clinpharm/ddis/main-table/

Table 6 Prohibited Medications (CYP3A Inhibitors and CYP3A Inducers)

Strong CYP3A Inhibitors	
indinavir	saquinavir
itraconazole, ,	ketoconazole
clarithromycin	nefazodone
ritonavir, ,	telithromycin
nelfinavir	suboxone
Strong CYP3A Inducers	
carbimazole	phenobarbital
phenytoin	St. John's wort (hypericum perforatum)
rifampin (rifampicin)	

7.3 Medication to be used with caution

BGB-3111 is a weak 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 we believe that BGB-3111 does not clinically inhibit the drug concentration of these CYP isozymes, the investigators should be aware that BGB-3111 may have an effect on drugs that are metabolized by CYP2C8, CYP2C9 and CYP2C19. Examples of these medications include, but are not limited to those listed in Table 7, for a complete list please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/

Table 7 Medications to be used with caution (Substrates of CYP2C8, CYP2C9, and CYP2C19)

Substrates of CYP2C8	**Substrates of CYP2C9**	**Substrates of CYPC19**
Amodiaquine	**Oral anti-diabetes mellitus**	**Proton Pump Inhibitors**
cerivastatin	Tolbutamide	lansoprazole[1]
paclitaxel	glipizide	omeprazole[1]
Repaglinide	**Angiotensin II receptor blocker**	**Pantoprazole**
Sorafenib	Losartan	rabeprazole
torsemide	irbesartan	**Anti-epileptics:**
	sulfonylureas	Diazepam
	Glyburide	Phenytoin (O)
	Glibenclamide	S-mephenytoin[1,2]
	Glipizide	Phenobarbitone
	Glimepiride	**others**
	Tolbutamide	Amitriptyline
	others	Carisoprodol
	Amitriptyline	Citalopram
	Celecoxib	Chloramphenicol
	Fluoxetine	Nelfinavir
	Fluvastatin	Progesterone
	S-warfarin	Proguanil
		Propranolol
		R-warfarin

8 STUDY ASSESSMENT ON SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND OTHER PARAMETERS

All subjects must sign on informed consent before screnning. Table 3, Study Assessments and Procedures Schedule, shows specific study evaluations and procedures. Table 4 and Table 5 show the time points for pharmacokinetics and efficacy sampling.

8.1 Demorgraphy and Baseline Characteristics

Demorgraphy includes date of birth, race, height (cm), weight (kg), and body mass index (kg/m^2). When measuring height and weight, subjects can not wear shoes, allowing them to wear indoor daytime clothes. This data will be entered into the electronic case report form and database. After signing the informed consent form, the subject is requested to perform screening according to the criteria listed in section 5 to determine whether the subject is eligible to enter the study. In addition to the disease assessment, a screening evaluation will be completed within 28 days prior to the initial dose of study drug. As indicated in Table 3, the screening assessment completed within 72 hours of administration can be used as a baseline assessment. Screening assessments include:

Baseline demgraphic data

Medical history and baseline characteristics

Collect phathologic information, include predictors of subjects with CLL (del 17p, del 11q, del 13q and p53 mutation and IgVH mutation), CXCR4 and MYC88 mutation of subjects of WM.

Vital signs (systoic pressure, diastolic pressure, pulse, body tempreture and respiratory rate)

B-symptoms (body weight decrease >10% within 6 months without significant causes, fever >38 °C and/or night sweat)

General physical examination

ECOG performance score

Echocardiogram

12-lead ECG

Concomitant medication

Adverse event and serious adverse event recording

CT/PET or CT scan for tumor evaluation

Bone marrow examination

Complete blood count (section 17.0, appendix 1)

Clinical biochemistry (section 17.0, appendix 1)

Coagulation test (section 17.0, appendix 1)

Immunoglobulin serum IgA, IgG, IgM level and immunofixation electrophoresis（section 17.0, appendix 1）

Pregnancy test in women with childbearing potential

Serum viral test (HBV, HCB, HIV)

Urinalysis (section 17, appendix 1)

The above data will be included in source document, and if there is a result beyond the normal range, the investigator will decide case-by-case whether or not to repeat the assessment.

8.2 Assessment during treatment

Safety assessment will be conducted during each visit at study center and throughout the study. Table 3 lists the assessment schedule and procedure to be implemented.

8.2.1 Assessment at Laboratory of Study Center

Before giving study drug, laboratory test should be conducted at local lab on day 1. If assessments completed during screening is within 72 hours before the first dose, there is no need to repeat tests. Assessments to be performed are listed in section 17.0 appendix 1.

Clinical biochemistry analysis, complete blood count, coagulation test, urinalysis, immunoglobulin and immunofixation electrophoresis should be performed as scheduled in table 3.

If a subject experiences neutropenia (absolute neutrocyte count < 1000/mm^3), thrombocytopenia (platelet count < 50,000/mm^3), or grade 3 of clinical biochemistry toxicity, repeated tests should be conducted as per physician's judgement until toxicity has recovered to Grade ≤ 2. If necessary, related additional tests could be performed according to guidelines of hospital. All subjects who have grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until they have resolved to grade 1 or 2, unless these parameters can not be improved due to the disease itself.

In urine routine analysis, if urinary protein ≥ 2 +, a quantitative test of 24-hour urinary total protein will be performed. If the protein is > 2 g / 24 hours, the study drug will be discontinued until the urinary protein has resolved to ≤ 2 g / 24 hours (for subjects with Waldenstrom's macroglobulinemia, it should be determined by the doctor whether or not to discontinue). If the urine protein ≤ 2 g / 24 hours, further clinical examination or repeat test should be considered depending on clinical manifestations. All subjects with Waldenstrom's macroglobulinemia should undergo a first immunofixation electrophoresis during screening. If monoclonal protein (M protein) present, repeat tests will be conducted in the subsequent immunoglobulin tests.

8.2.2 Physical Examination, Vital signs, B-symptoms

A completed or targeted examination, viatl signs (systoic pressure, diastolic pressure, pulse, body tempreture and respiratory rate) examination, weight and B-symptoms measurements should be performed according to schedule in table 3, table 4 and table 5.

Systemic physical examination include cardiovascular system, respiratory system, abdomen, neurosystem, lymph node/spleen skin, oropharynx and limbs. Targeted examination mainly targets on clinical relevant systems (e.g. cardiovascular system, respiratory system, lymph node, liver and spleen) and clinical symptom /sign relevant system. B-symptoms includes unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or night sweat.

8.2.3 ECG

A 12-lead ECG will be performed in triplicate at screening, EOT or premature withdrawal. Subjects should be in the semi-recumbent or supine position in ECG examination.

ECG should be performed according to schedule in table 3, table 4 and table 5. It is required to perform ECG in triplicate at each PK sampling time points, but ECG is not needed at sampling time point of 0.5 hours after administration.

Significant prolonged QTc interval is defined as QTcF interval ≥ 500 msec, or QTcF interval ≥ 60 msec from baseline. For both cases, two or more ECG follow-up examinations should be performed and the interval between two ECGs should be at least 5 minutes. Moreover, it should be manually measured by a qualified doctor.

If a subject experiences significant prolonged QTc:

- Delay the administration of study drug
- Conduct a medical evaluation of the subject, give appropriate treatment, and then perform at least 3 ECGs per week until the QT and QTc intervals return to within 30 ms of the baseline level.

Consult medical monitor before resuming treatment.

Consult medical monitor before initiating higher dose.

8.2.4 CT Scan

Subjects need to undergo a tumor evaluation at the time of enrollment. If enlarged liver, spleen, lymph nodes or other abnormal clinical symptoms are detected, a contrast-enhanced CT examination must be performed within 7 days of the ends of Week 12, 24, 36, 48, and within 2 weeks of every 24 weeks end afterwards. Subjects with hairy leukemia should be evaluated within 7 days after Week 12, 24, 36, 48, and followed by local practice after one year. Contrast-enhanced CT scan (oral or IV contrast) can be used in tumor assessment, including neck, chest, abdomen and pelvic. In order to improve the resolution of CT scan, PET/CT scan can be used to accurately measure the lesions size of lymph nodes, liver, spleen. Investigators can also use MRI to replace CT. Investigator should judge if PET-CT is required during screening. For subjects who are positive for PET-CT during screening, it is necessary to repeat examination when confirming CR. Investigators at each study center should perform a related imaging study at each disease assessment. If a subject terminates the treatment prematurely and has not undergone CT scans within 3 months, a CT scan is also required at the time of termination.

8.2.5 Bone Marrow Examination

All subjects have to undergo bone marrow examination during the screening period. If the bone marrow examination had been performed 30 days before the screening period, the results could be used for screening without repeated

examination. For patients with Waldenström's Macroglobulin, if there is bone marrow lesion, bone marrow examination is required every six months. Patients who have been diagnosed with bone marrow lesions at the time of enrollment may need to undergo further bone marrow aspiration and biopsy to confirm if they are subsequently judged to be possible CR by a physical examination or CT scan.

8.2.7 Detection of Minimal Residual Disease (MRD)

For CR subjects, peripheral blood or peripheral blood plus bone marrow samples will be examined by flow cytometry (FCM) at least three months after study drug discontinuation to detect minimal residual disease (MRD).

8.2.8 Adverse Events

All adverse events and serious adverse events, regardless of causality, will be collected throughout the process from the time of signing the informed consent form to 30 days of follow-up after last administration.

8.2.8.1 Asymptomatic lymphocytosis induced by study drug is not recorded and reported as an adverse event

In this protocol, the study drug-induced lymphocytosis is defined as lymphocyte count increase by ≥ 50% compared to baseline and absolute count ≥ 5,000/μL, with at least one disease-related parameter (including lymph node size, spleen size), hematological parameters (hemoglobin or platelet count) or disease-related symptoms have improved significantly.

In view of the known mechanism of action of BTK inhibitors, the study drug-induced lymphocytosis is expected and may occur frequently. In this study, asymptomatic study drug-induced lymphocytosis (including the resulting WBC increase) would not be recorded and reported as an adverse event and would not affect the patient's continued treatment of the study drug.

8.3 Safety

Safety assessment parameters include vital signs, B-symptoms, clinical laboratory tests (hematology, clinical biochemical analysis, coagulation, urine analysis, immunoglobulin analysis, and immunofixation electrophoresis), 12-lead electrocardiogram and physical examination. Throughout the course of the study, the staff at the research center will follow-up the adverse events and grade the adverse events and toxicity according to NCI-CTCAE version 4.03.

8.4 Follow-up Assessment

At 30 days after the last administration, all subjects should be returned to the study center for final assessment. Table 3 lists the assessment items to be conducted.

Follow-up all abnormalities that are independent of disease progression until they have resolved to baseline level.

8.5 Efficacy Assessment

Efficacy is not a primary objective. However, the following efficacy end points will be assessed:

- Number and proportion of subjects who have achieved objective response or stable disease (complete response, partial response, and complete response + partial response)
- Clearance rate of minimal residual disease (MRD)

- Progression-free survival (PFS)
- The duration of complete response or partial response, and the duration being in stable disease.

The efficacy evaluation will be based on appropriate evaluation criteria (IWCLL-CLL[15,16], NCI-WG-NHL[17], IWWM-WM[18], as shown in section 17.0, Appendix 3). A CT scan (PET, if applicable) will be performed at the end of Week 12、24、36、48、72 and 96 of treatment, and bone marrow aspiration and/or biopsy will be performed at Week 12 of treatment and thereafter (if the subject has bone marrow lesions before enrollment and is suspected to achieve CR).

8.6 Pharmacokinetics

To understand the pharmacokinetic profile of BGB-3111 and possibly major metabolites, blood samples need to be collected. The amount of blood to be collected at each time point is approximately 4 ml for pharmacokinetic analysis. Table 4 and Table 5 show the sampling time points. The Center Laboratory Service Manual details operation instructions on handling pharmacokinetic plasma samples, including labeling and shipping instructions. As the study will continue to monitor the drug exposure, frozen plasma samples should be transported as soon as possible after collection.

In the event of dose-limiting toxicity (DLT) or other serious drug toxicity, blood samples (4 ml) need be collected to determine the BGB-3111 plasma concentration, drug-drug interaction, and other possible mechanisms, according to the opinion of the investigator after discussion with sponsor's medical monitor. Investigator must record the time of blood collection and the time of administration in the eCRF.

If it is suspected that BGB-3111 interacts with a concomitant drug, a further blood sample may be collected for pharmacokinetic analysis to describe the extent of drug interactions.

Appendix 2 describes the maximum amount of blood to be collected during the course of the study (including the safety assessment during the screening period).

8.7 Pharmacodynamics

The proportion of BTK occupied in peripheral blood mononuclear cells will be evaluated as a biomarker for the inhibition of BTK. For information of sample collection, handling, storage and transportation, please refer to the Center Laboratory Service Manual.

8.8 Molecular Markers

All subjects in Part II should provide a recent tumor specimen for molecular marker analysis. If the subject does not have a recent sample of tumor tissue, a fresh tumor biopsy must be performed during the screening period. The tumor tissue can be either formalin-fixed paraffin-embedded tumor tissue block or at least 10 unstained slides and sent to the central laboratory for analysis. For patients with follicular lymphoma or marginal zone lymphoma who have been enrolled under protocol 1.0, historical tumor specimens or samples need to be provided after voluntary signature of new informed consent. For detailed information on tumor tissue collection, please refer to the laboratory manual.

9 QUALITY CONTROL AND QUALITY ASSURANCE

Under the GCP, the sponsor is responsible for the implementation and maintenance of the standard operating procedures (SOP) system for quality assurance and quality control.

Quality control will be performed at all stages of data processing.

To ensure the accuracy, consistency, completeness and data reliability of the study, the following measures will be taken:

- Convene investigator meetings
- Verify the qualification of laboratory and check up the ECG results
- Conduct initiation visit to study centers
- First Patient Enrollment visit
- Regular monitoring
- Continuous communication and training of study centers
- Quality control of data management
- Continuous data acquisition and cleaning
- Internal data review
- Quality control checks for clinical study reports

In addition, the sponsor and the CRO's Quality Assurance will review the study process on a regular basis, including but not limited to study centers, central laboratories, suppliers, clinical databases, and final clinical study reports.

9.1 Study Monitoring

According to the relevant regulations, GCP and the requirements of the sponsor, the sponsor's monitor will conduct an on-the-site inspection of the study center before enrollment procedure, and also on-the-site monitor on a regular basis during the study period. The purposes of the monitoring activity include:

- Learn about study progress.
- Verify study data.
- Ensure of data traceability.
- Q & A for all questions.
- Ensure that the data is true, accurate and complete.

- Ensure that the safety and benefits of the subject are protected.
- The investigator agrees and allows the monitor to have direct access to all study documents and to discuss or answer any questions related to the study.

9.2 Data Management and Coding

The data generated by this clinical study will be processed according to the relevant SOPs of the company's data management and biostatistics departments.

This study will use an electronic data acquisition system in which the study center will transcribe all electronic case report data into a spreadsheet. Data collection will be performed by the authorized study center staff designated by investigor. Training and safety guidance for investigators and all authorized study center personnel should be provided prior to initiation of the study and before the subject data being entered into system.

The eCRF should reflect the latest observations of the subject. Therefore, the eCRF should be completed as soon as the subject visits or after treatment. In order to avoid data discrepancies between observers, try to ensure that all safety evaluations are performed by the same investigator from the initial baseline assessment to follow-up. The investigator must verify the accuracy and correctness of all the data entered into the eCRF. If some of the assessment items are not carried out, or if certain information is not available or is not applicable or is not known, the investigator should indicate in the eCRF. After the clinical data is collected, the investigator must confirm the contents by electronic signature.

The investigator will check the eCRF to assess its completeness and consistency. In order to ensure that there is no discrepancy between the key data, the eCRF will be tested for traceability with source documents. All records, corrections and changes to the eCRF are made by the lead investigator or its designated person(s). The monitor can not enter data in eCRF. Once the clinical data of the electronic case report form has been sent to the central server, any data modification will leave a correction trail (revision mark), i.e the reason for the change, the name of the reviser and the time and date of the change. Before the clinical data has been entered into the eCRF, the study center staff will be assigned corresponding rights. If data revisions are required, the monitor or data manager will question the data collected through the procedures, and authorized study center staff will respond to these questions.

The eCRF is essentially a data entry form and should not be treated as a raw (or source) medical record unless otherwise specified. The source file is defined as all documents used by the investigator or hospital related to the history of the subject, which demonstrate the presence of the subject, verify the inclusion and exclusion criteria, and cover all the records of the subject during the study period. The source files include laboratory records, ECG results, memos, drug dispensation records, subject files, and so on.

It is the responsibility of the investigator to maintain the source document. At each monitoring activity, these documents must be in a status that allows the monitor to check. The investigator must send a completed eCRF to each subject who receives the study drug, regardless of the duration being in the study. All supporting documents sent with the eCRF, such as laboratory or hospital records, should have a clear study identification code and a subject identification code. In order to protect the confidentiality of personal information, personal information including the name of the subject should be removed or omitted.

The electronic case report form will automatically add the unique user name of the creator as proof of identity. The investigator makes an electronic signature in the specified documents, indicating that he/she has checked the data and confirms its accuracy. Investigators use their unique user name and password for electronic signatures; for electronic signatures, the date and timestamp will be automatically added. If any records in the eCRF need to be changed, it should follow the relevant software flow. All changes will be fully documented in the protected audit trail and the reasons for the change will be clarified.

Adverse events will be encoded using the MedDRA 17.0, accompanying drug will be encoded using the World Health Organization's drug dictionary (WHO-DD), and accompany disease/medical history will be encoded using the MedDRA 17.0.

9.3 Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the sponsor may perform quality assurance audit(s). Regulatory authorities 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 for the audit/inspection, and discuss clinical findingsor any relevant issues.

10 SAFETY

10.1 Adverse Event (AE) and Serious Adverse Event (SAE)

An AE is defined as any unfavorable medical occurrence after patient or subject signing informed consent, regardless of whether it is related to the study drug.

A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is significant medical event requiring intervention.

If an adverse event occurs during the trial, the investigator or the lead investigator must give proper treatment immediately and explain to the subject. Adverse events must be followed until the subject has returned to normal or the investigator considers that the follow-up is no longer needed.

Table 7: definition of serious adverse event

Death	Adverse event(s) cause death of the subject, except for death due to disease progression
Life-threatening	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.
Hospitalization	Adverse event leads to hospitalization, excluding emergency treatment or out-patient visit.
Prolongation of existing hospitalization	Adverse event occurs during hospitalization and make the hospitalization longer than expected.
Congenital abnormality	Found deformity at birth or after birth, or any deformities result in abortion.
Result in permanent or significant disability /dysfunction	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.
Significant medical event requiring medical intervention	Significant medical event that will not cause immediate death or threat life or lead to hospitalization at the time of event, but it may jeopardize the subject or may require medical/surgical intervention to present one of the outcomes listed above

10.2 Timeframe for Adverse Event

All adverse events and serious adverse events will be collected from signing the informed consent until 30±7 days after treatment discontion, either report by investigator or spontaneously report by subject.

After signing the informed consent, serious adverse events that occur prior to the initiation of study drug but relate to the operation (e.g. biopsy) required by the protocol should also be reported.

After more than 30 ± 7 days after discontinuation of the study treatment, the investigator should report a serious adverse event that is considered to be related with the study treatment.

The investigators should judge the adverse events by asking the subjects for non-induced questions.

10.3 Documentation of Adverse Event

Investigator should use medical terminology/definition to record AE or SAE. Oral and abbreviations should be avoided. All AE (including SAE) should record in source document and AE pages in CRF.

Diagnosis, symptoms and signs

If a diagnosis has been made, the diagnosis should be recorded on the CRF rather than the individual symptoms and signs (eg, liver failure, not jaundice, elevated transaminase, and flapping). However, if the symptoms and signs can not be classified as an individual diagnosis at the time of the report, each individual event should be recorded on the CRF as AE or SAE. If later diagnosed, it should be reported as follow-up information.

Adverse event secondary to other event

In general, primary events should be recorded for adverse events secondary to other events, such as those caused by other events or clinical sequelae, unless the secondary event is severe or serious adverse events. However, secondary events with significant clinical significance should be recorded as independent adverse events in the source document and CRF if the time of occurrence of the primary event is different. If the association between events is unclear, they should be recorded separately both in the source documents and CRF.

Persistent or recurring adverse events

Persistent adverse events refer to adverse events that persist and have not been alleviated between two time points of the subject. This adverse event should be recorded only once on the source document and CRF. The initial severity of the event should be recorded and updated when the event is aggravated to record the most serious degree of the event.

Recurrence of adverse events refers to the adverse events that have been alleviated between two time points, but have occurred later. The occurrence of the event should be recorded separately in the source document and the CRF.

Laboratory abnormalities or abnormal vital signs

Not all laboratory abnormalities/vital signs should be reported as AE. Only laboratory abnormalities/abnormal vital signs that meet the following criteria should be reported as AE:

- With clinical symptoms.

- Lead to changes in study treatment (e.g dose adjustment, interruption or permanent withdrawal, etc.).
- Requires medical intervention or changes in combination therapy.
- Judged by investigator have a significant clinical significance.

It is the responsibility of the investigator to review all laboratory abnormalities and abnormal vital signs and to conduct medical judgments whether each laboratory abnormality or abnormal vital signs should be reported as AE.

If laboratory abnormalities or abnormal vital signs with clinical significance is actually manifestations of a disease or syndrome (such as alkaline phosphatase and bilirubin increased to more than 5 times the normal upper limit caused by cholecystitis), only the diagnosis (ie, cholecystitis) is recorded on the source document and the AE page of the CRF. On the contrary, laboratory abnormalities or abnormal vital signs should be recorded on the source document and the AE page of CRF, and indicate that the test value is above or below the normal range (e.g it should be recorded as "elevated serum potassium" instead of "Abnormal serum potassium"). If laboratory abnormalities or vital signs have corresponding standard clinical terms, then clinical terms should be recorded in the source document and CRF. For example, serum potassium increased to more than the normal upper limit should be recorded as "hyperkalemia."

The same clinically significant laboratory abnormalities or vital signs found in multiple follow-up visits should not be recorded as AE or SAE for multiple times no matter in the source document or CRF unless there is a change in severity or etiology.

Death

All deaths occurring during the entire trial, including the follow-up period of 30±7 days after the last administration, whether or not related to the study drug, should be recorded in the source document and death report form in CRF and reported to the sponsor in a timely manner.

In the event of a death event, if there is an adverse event leading to death, an individual medical term should be used to record the death event in the source document and the AE page of CRF, and this event should be reported as an SAE in Accelerated Report; if the cause of the death is unknown at the time of report, it should be recorded in the source document and AE page of CRF as "unexplained death", and firstly report as so in SAE accelerated report, then further investigate the exact cause of death; if death is caused by tumor progression , it will not be recorded and reported as AE/SAE, but the investigator should record the death in the death report form of CRF, and promptly inform the sponsor.

Pre-existing medical condition

Symptoms/signs that have been present in the trial screening period should be recorded and reported as adverse events only if therer is an increase in severity, frequency, and nature (except for the deterioration of the disease condition under study). Changes relative to baseline, such as "increase in headache frequency", should be reflected in the record.

Requires hospitalization or prolongation of existing hospitalization

Any adverse events that result in hospitalization or prolongation of existing hospitalization should be recorded and reported as SAE, with the following exceptions:

- Planned hospitalization or prolongation of existing hospitalization according to protocole (e.g for administration, efficacy assessment, etc.).
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline, such as elective surgery/treatment scheduled before participation in the study. However, if the pre-existing disease has been deteriorated in the study (e.g requires surgery/treatment earlier than originally planned), elective surgery/treatment that is required due to the deterioration of the disease will be considered an adverse event.
- Hospitalization due to routine or social reasons or hospitalization by reasons other than adverse events, is not considered an adverse event.

Pregnancy

If a female subject become pregnant during study, study drug should be discontinued immediately and investigator should be informed promptly. Investigator should report to sponsor within 24 hours. The investigator should discuss with the subject the risk of continuing pregnancy and the possible impact on fetus. The monitoring of the subject should continue until end of pregnancy. Pregnancy within 30 ± 7 days of the last dose should be reported to investigator.

Whether induced abortion or spontaneous abortion, it should be recorded and reported as SAE. A baby born to a female subject who has taken study drug or the female partner of a male subject should be recorded and reported as SAE if any congenital abnormality/birth defects exists.

Medication error, overdose, abuse and misuse

If medication error, overdose, abuse and misuse of study drug experienced by subjects, it should be reported to sponsor within 24 hours of investigator's knowledge. If above situations lead to SAE, investigator should report the SAE, and situations such as medication error need not to be reported in a separate report.

Liver function abnormal

ALT or AST increase to more than 3 times the baseline value with total bilirubin increase to more than 2 times the normal upper limit and ruled out clinical jaundice induced by cholestasis or other cause is considered a sign of severe liver injury. Therefore, investigator must report following cases as adverse events:

- During treatment ALT or AST increase to more than 3 times the baseline with total bilirubin increase to more than 2 times the normal upper limit (35% of the direct bilirubin).
- During treatment ALT or AST increase to more than 3 times the baseline with clinical jaundice.

The most appropriate diagnosis, or laboratory outliers when the diagnosis is not established should be recorded in source document and the AE page of CRF, and report to sponsor within 24 hours after knowledge of the event, whether or not it is serious Adverse events.

Disease progression

The disease studied in this study, or the expected disease progression, or the symptoms or signs induced by disease progression, will not be reported as an adverse event unless it is more severe than expected.

Lack of efficacy

When the disease treated by the study drug is deteriorating, it may not be possible to determine whether it is a lack of efficacy or an adverse event. In this case, unless the investigator judges that the deterioration of the disease is related with the study drug, or such change is considered lack of efficacy rather than adverse events.

10.4 Assessment of Causality

The relationship between the study drug and adverse event(s) or the role of study drug in adverse event(s) can be judged by the following classification and criteria:

1) Definitely related

The reference criteria are as follows: there is a reasonable temporal relationship between adverse events and drug administration; events can not be explained by underlying disease or other drugs; de-challenge reaction is confirmed positive; adverse events are consistent with the pharmacological properties of the drug and, if necessary, plus positive re-challenge.

2) Probably related

This category applies to those adverse events that are highly determined to be related with the study drug. The adverse event would be considered to be relevant if the following three or more are met:

a) Has reasonable temporal relationship.

b) Can not be reasonably explained by the known clinical symptoms and signs of the subject, the environmental or toxic factors, or other treatment received by the subject.

c) Adverse event disappears or alleviates after discontinuation or reduction of dose.

d) Be consistent with known toxicity of suspect drug.

e) Adverse events recur after re-challenge.

3) Possibly related

This category applies to adverse events that has uncertain but not positively excluded relationship with the study drug. If the following 2 or more are met, it is considered that the adverse event is likely to be relevant:

a) Has reasonable temporal relationship

b) May be caused by the disease, environmental or toxic factors of the subject or other treatment received by the subject.

c) Be consistent with known toxicity of suspect drug.

4) Possibly unrelated

Usually this category applies to adverse events meeting two or more of the following criteria:

a) Unreasonable temporal relationship.

b) Adverse event is obviously caused by subject's disease, environment or toxic factors or other treatment received by subjects.

c) Inconsistent with toxicity of suspect drug

d) No recurrence or aggravation of adverse event after rechallenge.

5) Unrelated

This category applies to adverse events obviously caused by other factors such as disease or environment. And it is inconsistent with all above criteria.

10.5 Adverse Events Which Cannot be Graded According to CTC

When completing the AE Form in eCRF, the investigator should refer to the five-grade scale developed from NCI CTC-AE version 4.03. For adverse events that can not be classified according to CTC, the severity of each adverse event will be graded by the clinical description, as follows:

- Grade 1: Mild; asymptomatic or with slight signs; only with clinical or diagnostic observations; no medical intervention needed.
- Grade 2: Moderate; requires minimal, local or non-invasive treatment, age-appropriate daily life functions (e.g. cooking, shopping, using phone, financial, etc) are limited.
- Grade 3: serious or clinically significant but not immediately life-threatening; hospitalization or prolonged existing hospitalization; disabled, daily self-care (e.g. bathing, wearing clothes, eating, toilet, medication) limited, but not bed-ridden.
- Grade 4: leading to life-threatening consequences; emergent treatment is required.
- Grade 5: adverse event related to death.

10.6 Management of Adverse Event

10.6.1 Report of Adverse Event

The investigator needs to evaluate and record any of the adverse events in detail, including the onset date, symptoms, severity, duration and outcome, the relationship between the adverse event and the study drug, diagnosis and the measures taken. The investigator should provide other explanations for serious adverse events that possibly unrelated or unrelated to the study drug.

10.6.2 Report of Serious Adverse Event

For serious adverse events (or pregnancies) that occur during the study period up to 30 ± 7 days after the last administration, the investigators must report it to the sponsor within 24 hours of knowledgement, regardless of whether the subject has received treatment. The investigator shall submit the event report to the regulatory authorities or the ethics committee in accordance with relevant regulations. Serious adverse events occurring outside the above-mentioned period, if considered to be related with the study drug, should also be reported to the sponsor.

10.7 Follow-up of Adverse Event

Adverse events related with the study drug should be followed up until the event returns to baseline or being stable. If adverse events can not be resolved to the baseline level or being stable, a reasonable explanation should be recorded in the source document and CRF. Regardless of whether the event is related to the study drug, all serious adverse events need to be handled properly until the lead investigator or investigator determines that the event is chronic or stable, or that the event is finally determined to be unrelated to the study drug or relevant procedures. The recovery and date of AE or SAE should be recorded in source document and CRF.

10.8 Pregnancies

10.8.1 Pregnancy Test

For women with childbearing potential, serum pregnancy test will be performed during the screening period, and the urine pregnancy test will be performed according to the time points specified in Table 3. Pregnant female subjects are not allowed to participate in this study. If the pregnancy test is positive at any time during the study period, the female subject should immediately withdraw from the study.

The results of the pregnancy test need to be entered into the database.

10.8.2 Time Period to Collect Pregnancy Information

The time period for collecting the pregnancy information is from the screening period until follow-up of 30 ± 7 days after the last dose. It is not necessary to report the pregnancy information confirmed before the start medication to the sponsor.

10.8.3 Management to Pregnancy

After receiving the study drug, if the subject's pregnancy test is positive at any time, the subject should be immediately withdrawn from the study. When the study is discontinued, all relevant test results should be collected as baseline assessment.

The investigator or his authorized personnel is responsible for collecting pregnancy information about female partners who are pregnant or male subject’s female partner who are pregnant during the study. The investigator or his authorized personnel should properly record the pregnancy information and complete the pregnancy report form within 24 hours of knowledgement and submit it to the sponsor, and follow up the pregnancy to collect the outcome. Report to the sponsor of any early termination of pregnancy or mother and child status information. In general, the follow-up period does not exceed 6 to 8 weeks after the expected date of delivery.

Although the occurrence of pregnancy is not considered an AE or SAE, but the pregnancy complications or non-urgent pregnancy termination for medical reasons will be recorded as an AE or SAE and will be followed.

Spontaneous abortion is considered a SAE and will be reported. In addition, for serious adverse events that occur as a result of pregnancy after withdrawal from the study, the investigator should reasonably consider the event to be related to the study drug and report the event to the sponsor. Although the investigator has no responsibility to actively collect information about spontaneous abortion in previous subjects, he/she may be informed of serious adverse events through spontaneous reporting.

11 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

11.1 Sample Size Consideration

Part I (dose safety assessment): The final sample size will depend on the amount of dose level to be evaluated and DLT of each dose group. It is estimated that 20 subjects will be enrolled to complete the dose selection of BGB-3111 monotherapy in Chinese subjects with B cell malignant lymphoma. Study data will be sorted and analyzed according to statistical plan.

Part II (dose expansion): approximately 20 subjects with relapsed and refractory follicular lymphoma or marginal zone lymphoma will be enrolled to assess anti-tumor activity of BGB-3111. Study data will be sorted and analyzed according to statistical plan.

11.2 General Guideline for Data Analysis

All statistical analyzes will be performed using SAS® Version 9.2 higher (Statistical Analysis System, SAS Institute, Inc., Cary, North Carolina), unless otherwise indicated.

11.2.1 Data Analysis Population

The Safety Population includes all subjects who received BGB-3111. The PK population includes all treated subjects with evaluable BGB-3111 PK parameters. Other evaluable parameters will be listed in statistics report.

Detailed statistics method will be illustrated in statistics plan.

11.2.2 Study Analysis

Two analyses will be conducted according to study schedule. The first analysis will be conducted after all enrolled subjects have completed a dose-limiting toxicity (DLT) assessment, and this analysis will focus on assessing the safety and tolerability of BGB-3111. Pharmacokinetic and pharmacodynamics analysis will be included in this analysis if data is available. RP2D will be based on the results of the first analysis. Study will be completed if all subjects experience disease progression, intolerance to toxicity, death, withdrawn from study, termination by sponsor or having completed all 3-year treatment. The primary analysis will be conducted after the end of study, including the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of both regimens of BGB-3111. The results of these analyzes will be included in the clinical trial report.

11.3 Efficacy Analysis

Efficacy is not the primary objective of the Part I portion of this study. The efficacy evaluation will be based on appropriate evaluation criteria (IWCLL-CLL[15, 16], NCI-WG-NHL[17], IWWM-WM[18], as described in Appendix 3, Section 17.0). Database and classified synopsis will be provided if data validation needed.

The progression-free survival (PFS) (defined as the time from the starting date of BGB-3111 to the date of first documentation of disease progression or death, whichever occurs first) would be estimated using the Kaplan-Meier method, with a median and 95% confidence Interval.

The objective response rate (ORR), the complete response rate (CRR), will be assessed with 95% confidence interval. The duration of response (DoR) will be estimated using the Kaplan-Meier method.

Detailed statistical methods will be described in detail in the statistical plan.

11.4 Safety Analysis

Any subjects who have received at least one dose of BGB-3111 will be included in the safety analysis (ie, the safety assessment population). The safety is evaluated by a summary of changes in adverse events, changes in laboratory findings, and changes in vital signs. Adverse events obviously caused by disease progression were not included in the drug-related toxicity assessment.

Adverse events of special interests (such as bleeding) will be defined in the statistical plan.

Adverse events will be counted on individual subject and treatment group. All adverse events will be graded according to NCI CTCAE (version 4.03). The adverse events will be coded using the International Medical Dictionary (MedDRA 17.0 or higher). According to the System Organ Classification and the corresponding Preferred Term to sum up the number and frequency of adverse events. All SAE (including death), DLT, adverse events leading to withdrawal will be counted.

The safety data will be summarized according to the dose at which the subject is randomly assigned at the time of enrollment. For subjects with a dose increase or decrease, the adverse events that occurred will still be counted according to the assigned initial dose level group.

For laboratory parameters, hematology, blood biochemistry, coagulation, urine routine analysis will be listed one by one and indicate increase or decrease compared with the normal range. The laboratory results before and after administration will be compared and analyze the reason for the increase or decrease, if appropriate

11.4.1 Analysis of Dosage

The dosage analysis will be applied to all subjects treated with BGB-3111, and all doses will be analyzed according to medication status, withdrawal, dose adjustment, etc.

11.4.2 Electrocardiogram

ECG analysis of all subjects, including QT interval (QTc) and changes relative to baseline levels, will be analyzed case-by-case and indicate corresponding dosage level and assessment time. To explore the relationship between QTc interval and dose level, QT interval will be calculated using QTcF formula. The changes in QTcF (baseline corrected QTcF) for

each subject and the BGB-3111 blood exposure at the same time point will be analyzed separately for the Day 1 Week 1 and Day 1 Week 2, and if possible, a graphical or statistical approach will be used to investigate the potential correlation.

11.5 Pharmacokinetic Assessment

The time point of the pharmacokinetic sampling can be determined according to the pre-test. The blood sample will be collected after single dose of Day 1 and Day 2 of Week 1, after multiple doses on Day 1 Week 2, Day 1 Week 5, and Day 1 Week 9 (refer to Table 4 and Table 5).

Pharmacokinetic parameters of BGB-3111 will be analyzed as listed below:

$AUC_{0-\infty}$	Area under the plasma concentration-time curve for 0-∞
AUC_{last} and AUC_{ss}	Area under the plasma concentration-time curve for 0-final sampling time point and for steady state
C_{max} and $C_{max,ss}$	Maximum plasma concentration and concentration at steady state
t_{max} and $t_{max,ss}$	Time to maximum plasma concentration and time to steady plasma concentration
λz	Elimination rate constant
$t_{1/2}$	Half life
CL/F	Apparent plasma clearance
Vd/F	Terminal apparent distribution volume
RAUC	AUC accumulation (AUC of Day 1 Week 2/AUC of Day 1 Week 1)
RC_{max}	Accumulation of maximum plasma concentration (C_{max} of Day 1 Week 2/C_{max} of Day 1 Week 1)

If possible, the following pharmacokinetic parameters will be calculated using the list instead of descriptive statistics

Interval	Interval (hours) to determine the λz logarithm linear regression
n	Number of data points to determine λz logarithm linear regression (at least 3 points)
Rsq	Calculate the square of the λz correlation coefficient, and if the square of the correlation coefficient is less than 0.800, then λz and the relevant parameters will not be reported.
%AUCex	The percentage of AUC is calculated using extrapolation, and if more than

20%, AUC and related parameters will not be reported

Other pharmacokinetic parameters that need to be estimated.

The BGB-3111 plasma concentration-time data will be summarized by figures and tables, and will be analyzed based on non-compartmental model and/or compartmental model.

The pharmacokinetic parameters AUC_{last}、$AUC_{0-\infty}$、C_{max}、t_{max}、$t_{1/2}$、CL/F、Vd/F for single dose and AUC_{ss}、$C_{max,ss}$、$t_{max,ss}$ for multiple doses at steady state will be evaluated. The variables obtained at different time points will be statistically described by dose group. If the data is sufficient, the parameter values (mean, standard deviation, median, minimum, maximum, standard deviation and logarithm of geometric mean) for all treatment groups and each dose group will be described separately in the summary report.

The dose proportionality of AUC_{ss}、C_{max}、 and $C_{max,ss}$ of BGB-3111 will be evaluated using a power model in an explicit chart form. The statistical analysis of the relationship between the dependent variables (logarithm of PK parameters AUC, C_{max}, and AUC_{last}) and the independent variables (logarithm of dose) will be performed in a linear regression model ($\log [PK] = \alpha + \beta * \log [Dose]$), thus the model parameters [β] [α] will be estimated using least squares regression analysis. Dose proportionality with two-sided 95% confidence interval of regression coefficient will be estimated with power function model of at least 3 cases with effective pharmacokinetic parameters.

11.6 Pharmacodynamics Assessment

Pharmacodynamics is not the primary objective of this study. BTK occupancy proportion in peripheral mononuclear cell with by analyzed with samples collected at scheduled time points specified in Table 3 and Table 4.

11.7 Sample Size in Part II

20 subjects with relapsed and refractory follicular lymphoma or marginal zone lymphoma will be enrolled in Part II of dose escalation study. The sample size calculation is primarily based on the accuracy level of the overall response rate estimate. If the overall response rate is 35%, the 95% exact confidence interval would be (15.4%, 59.2%), thus the anti-tumor activity of BGB-3111 in refractory follicle Lymphoma or marginal zone lymphoma will be clearly demonstrated.

12 ETHICAL CONSIDERATIONS AND INFORMED CONSENT

12.1 Approval from Regulatory Authority

The sponsor should obtain a clinical trial approval from CFDA according to relevant regulations before the study is initiated at a study center.

12.2 Ethical document and Ethical 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, to best protect subjects.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol and amendments, informed consent form and any other information that will be presented to potential subjects (e.g advertisements for recruitment) as well as other necessary documents are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. The approval of the IEC/IRB must be obtained before the study starts and the committee's meeting and approval date should be indicated in the approval letter to investigators.

Any revision of the protocol must be formally approved or filed by the IEC/RB.

During the study, if any protocol violation may increase the risk of the subject, investigators should report to the IEC/IRB promptly.

12.3 Informed Consent

Subjects must sign informed consent before enrollment, and the process of signing informed consent will follow the relevant regulations.

12.4 Investigator Reporting Requirements

As described in Section 10.6, the investigator or sponsor should report all serious adverse events to relevant ethics committee and regulatory authorities in accordance with relevant regulations. In addition, investigators need to report updated safety reports and center closure notifications to the IEC/IRB on a regular basis during the course of the study, and the responsibility of such periodically reporting rests on the investigator instead of the sponsor.

13 PROTOCOL MODIFICATIONS

All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented, unless this modification is intended to reduce immediate risk to subjects, or only involve with administrative information change (such as telephone number change).

14 RETENTION OF STUDY FILES, CRF AND RECORDS

14.1 Retention of Study Files and Document

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 includes the protocol/amendments, CRF and query forms, IRB/IEC, and regulatory approval with correspondence, sample of informed consent, drug inventory form, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject's source documents (usually defined in advance to record key efficacy/safety parameters) include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, CT, X-ray, PET report, pathology and special assessment reports, signed ICF, consultant records, screening and enrollment log, etc.

Investigators need to reserve the documents for 5 years after completion or termination of study. Documents could be destroyed in accordance with the laws and regulations five years after study completion. Sponsor should be notified before documents destroyed.

The investigator must notify the sponsor of any changes in the archival arrangements.

If the investigator cannot guarantee this archiving requirement at the study center 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.

14.2 Source Document and Data

If the CRF is ambiguous or an error occurs in the data transfer, investigator should provide the original data in the study document or the medical record at the request of sponsor. If there is a special question, query from regulatory authorities and/or request during inspection, complete study records should be provided with protection of subject's privacy.

14.3 Audit and Inspection

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

14.4 Case Report Form (CRF)

For each subject enrolled, a CRF must be completed and signed by the principal investigator or designated personnel 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 due to DLT, every endeavor should be made to clearly document the outcome.

All CRF must be written with ballpoint pen which is not easy to fade. When making any necessary corrections, draw a line on the incorrect records rather than smear, and write down the correct content, the abbreviated signature and date of the investigator or designee.

15 UTILIZATION AND PUBLICATION OF RESEARCH DATA

15.1 Utilization of Study Data

All data of BGB-3111, such as patent application, dosage form, manufacturing process, basic research data, etc. is regarded as confidential information as long as it has not been published.

Data obtained from study is regarded as confidential informal as well. BeiGene will publish data to other clinical researchers, the state food and drug administration, or other government agency when appropriate. To ensure the integrity of the clinical data analysis, the investigators have an obligation to offer complete test results and data to sponsor.

Investigators must ensure that the privacy of the subjects is not disclosed to any unauthorized third party. The names of the subjects should not be included in submitted CRF and other file does, but only identified with a code. Investigator could retain enrollment form which includes identify code, name and address of subjects. Informed consent form and other documents should be strictly confidential, and not be submitted to sponsor.

15.2 Publication

The results of this study can be published in core journals. Investigator who provides major contribution to the implementation and management of the study, and employee who provides major contribution to the study design, explanation or analysis can be signed.

BeiGene promises to submit paper to investigator for review before publication of any study data. Investigators must obtain approval from sponsor before posting the academic paper or abstract. Investigator has the right to publish the results of this study but should comply with the protection of confidential information.

Confidential information of the intellectual property rights belong to BeiGene. Without written consent from BeiGene, confidential information shall not be disclosed to others or used for intertions except for this study.

16 REFERENCES

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17 APPENDIX

Appendix 1: Clinical Laboratory Test

Clinical biochemistry	Hematology	Coagulation	Urinalysis	Immunoglobulin analysis and immunofixation
Alkaline phosphatase	Hemoglobin	Prothrombin time	pH value	IgA
Alanine aminotransferase	Reticulocyte count Optional test	Activated Partial thromboplastin Time	Specific gravity	IgG
Aspartate aminotransferase	Platelet counts	International Normalized Ratio	Glucose	IgM
Albumin	WBC count with differential		Protein	immunofixation [2]
Total and direct bilirubin	Neutrophil count		Ketones	
CO_2（Carbon dioxide）	Eosinophil count		hematuria	
Blood urea nitrogen	Lymphocyte count		24-hour protein[1] Random urine protein	
Calcium	Bands Optional test			
Chlorine				
Creatinine				
Glucose				
Lactate dehydrogenase				
Phosphate Optional test				
Total protein				
Potassium				
Sodium				
Magnesium				
Phosphorus				
Uric Acid				
creatinine clearance				

1. If urine protein is ≥2+ in urinalysis, a 24-hour urine protein will be detected with calculation of random urine protein to creatinine ratio.
2. All subjects with WM will receive the first immunofixation. If monoclonal protein exists, all immunoglobulin will be detected.
3. It is not considered as a protocol deviation in case that a site cannot provide all examination results but it has no impact on drug safety assessment and with approval from medical monitor.

Appendix 2: Sample Collecting Volume

Time	Parameters to be assessed	Blood collection volume (mL) in Part I	Blood collection volume (mL) in Part II
Screening			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Coagulation test	3	3
	IgA, IgG, IgM level and immunofixation electrophoresis	5	5
	Serum virus detection	5	5
	Total volume	20.5	20.5
Week 1 Day 1			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Coagulation test	3	3
	Pharmacokinetics [1]	32[2]	36[2]
	Pharmacodynamics	16[2]	
	Total volume	58.5	46.5
Day 2			
	Pharmacokinetics [1]	4[2]	4[2]
	Pharmacodynamics	8[2]	
	Total volume	12	4
Week 2 Day 1			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Pharmacokinetics [1]	28[2]	36[2]
	Pharmacodynamics	8[2]	
	Total volume	43.5	43.5
Week 3 Day 1			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Total volume	7.5	7.5
Week 5 Day 1			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Coagulation test	3	3
	IgA, IgG, IgM level and immunofixation electrophoresis	5	5
	Pharmacokinetics [1]	4	4
	Total volume	19.5	19.5
Week 7 Day 1			
	Biochemistry	5	5
	Heametology	2.5	2.5
	Total volume	7.5	7.5
Week 9-53 Every 4 weeks			
	Biochemistry	5	5

	Heametology Coagulation test IgA, IgG, IgM level and immunofixation electrophoresis Pharmacokinetics [1]	2.5 3 5 4	2.5 3 5 4
	Total volume	19.5	19.5
Week 53 + Every 8 weeks	 Biochemistry Heametology Coagulation test IgA, IgG, IgM level and immunofixation electrophoresis	 5 2.5 3 5	 5 2.5 3 5
	Total volume	15.5	15.5
Treatment discontinuation or premature withdrawal	 Biochemistry Heametology Coagulation test IgA, IgG, IgM level and immunofixation electrophoresis	 5 2.5 3 5	 5 2.5 3 5
	Total volume	15.5	15.5

[1] When a safety event needs to be assessed for a relationship with drug exposure, the pharmacokinetic sample will be collected at any time without prior planning.

[2] Intravenous indwelling needle may be preset for collecting pharmacokinetic and pharmacodynamics samples. Samples will be collected through the intravenous indwelling needle at time points specified in table 4. Discard 1 ml of blood sample before each sampling.

[3] Only pharmacokinetic blood sample will be colllected on Day 1 Week 9.

Appendix 3: Efficacy Assessment Criterion

A) Chronic lymphocytic leukemia [15,18]

Parameters	CR*	PR	PD
Group A			
lymphadenopathy	None > 1.5 cm	Decrease by ≥50% and no new lymphadenopathy（> 1.5 cm）	Increase by ≥50% or new lymph node lesion
hepatomegaly	None	Decrease by ≥50% if liver enlarged at baseline	Increase by ≥50%
splenomegaly	None	Decrease by ≥50% if spleen enlarged at baseline	Increase by ≥50%
Blood lymphocytes	< 4000/μl	Decreasse by ≥50% from baseline	Increase by ≥50%** from baseline
Marrow	No clonal CLL cell infiltration, no nodular lymphocytes aggregate		
Group B			
BPC	> 100 000/ μl	> 100000/ μl or increase by ≥50% from baseline	Decreasse by ≥50% from baseline
Hb	> 11.0 g/dL	> 11.0 g/dL or increase by ≥50% from baseline	Decreasse by > 2g/dL from baseline
ANC	> 1500/ μl	> 1500/ μl or increase by ≥50% from baseline	

Criteria in Group A define the tumor load; Criteria in Group B define the function of hematopoietic system (or marrow).

CR (Complete reaponse): complies with all criteria and with no disease-related systemic symptoms.

PR (Partial response): ≥ 1 criteria in Group A plus ≥ 1 criteria in Group B. Persistent lymphocytosis does not affect the diagnosis of PR, which can be labelled PR-L.

SD (Stable disease): do not meet the criteria for partial response or progressive disease.

PD (Progressive disease): ≥ 1 criteria in Group A or ≥ 1 criteria in Group B.

* CRi: Compliance with all CR criteria, but there may be persistent neutropenia, anemia or thrombocytopenia that may be associated with drug toxicity instead of disease.

** In the context of reduced lymph node volume, mitigated organ enlargement, or improved hemoglobin/platelet count, isolated progressive lymphocytosis will not be considered progressive disease.

B) Lugano criteria for Non Hodgkin Lymphoma response assessment (PET should be completed with diagnostic contrast enhanced CT at the same time or proceed with different programs. [17]

Response	**Site**	**Pet-CT (metabolic response)**	**CT (Radiologic response)[d]**
Complete response	Lymph nodes and extralymphatic sites	Score of 1,2,or 3[a] on 5-point scale, with or without a residual mass [b,c]	All of the following: Target nodes/nodal mass 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 in morphology; if indeterminate, IHC negative
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	All of the following: ≥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 5mm 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
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy is 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	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 lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease	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	Progressive disease requires at least 1 of the following PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	unmeasurable lesions	None	Clear progression of new or pre-existing unmeasurable lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than other etiology (eg, infection, inflammation). If the etiology of new lesions is uncertain, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a] A score of 3 in many patients indicates a good prognosis, especially if at interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under-treatment).

[b] Refer to PET 5PS (5-PS)

[c] Generally, the uptake in Waldeyer's ring or sites of high psysiological uptake or spleen/bone marrow activation (e.g., by chemotherapy or myeloid colony stimulating factor) may be greater than that of normal mediastinum and/or liver. In this case, if the uptake of initially involved site is not greater than the surrounding normal tissue, even if this site is of high physiological uptake, it can also be judged as complete molecular response (CMR).

[d] It is possible to observe false positive PET scan results associated with infectious or inflammatory conditions. Biopsy in the affected area is still the gold standard for confirming new or persistent lesions.

PET 5-point scale (5-PS):

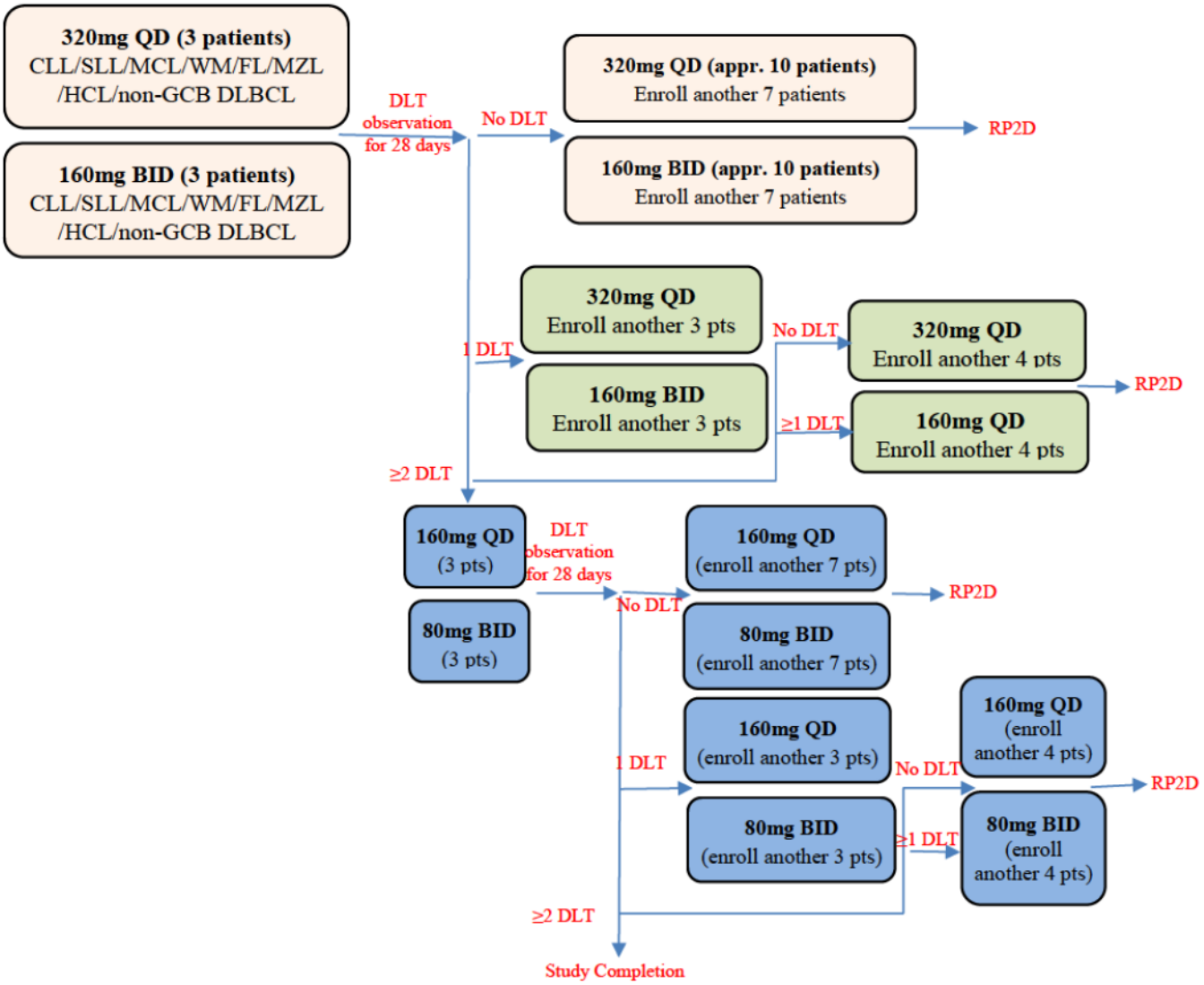
1. no uptake above background
2. uptake ≤mediastinum
3. uptake >mediastinum but ≤ liver
4. uptake moderately > liver
5. uptake markedly higher than liver and/or new lesions

X. new areas of uptake unlikely to be related to lymphoma.

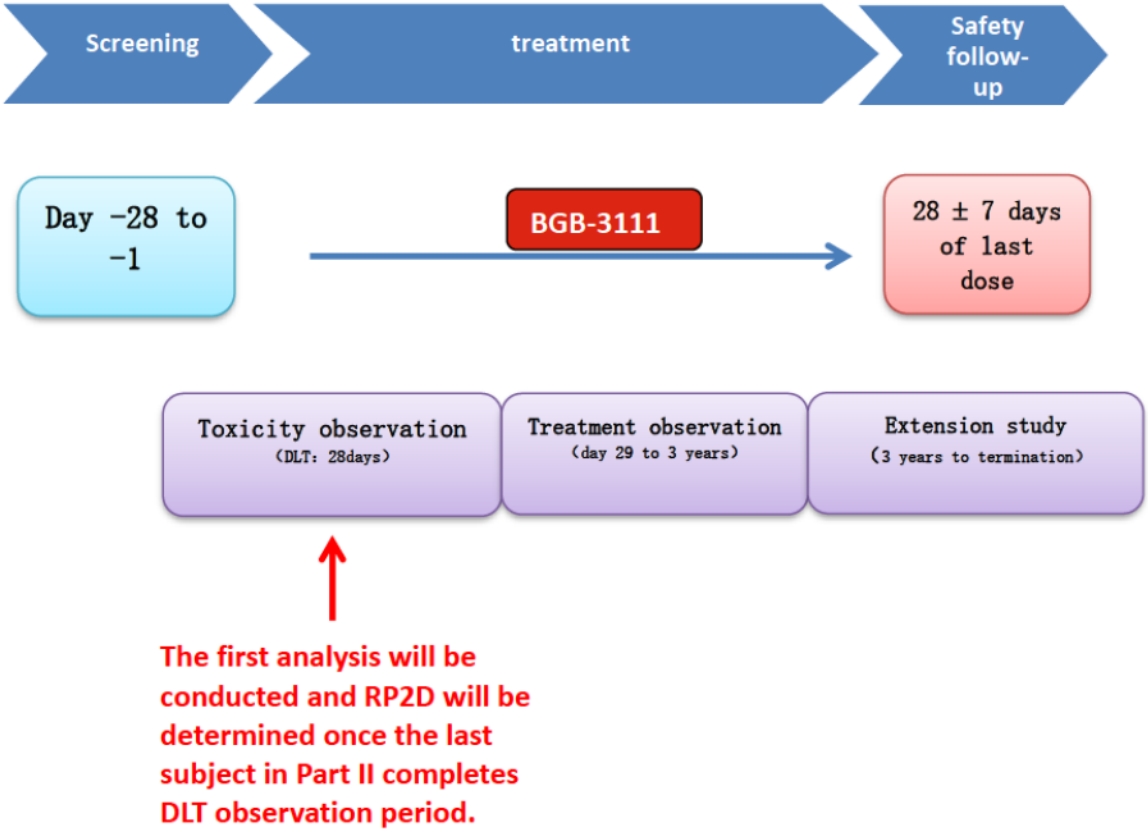
C) Waldenström's macroglobulinemia [18, 24]

- Complete response (CR): Absence of serum monoclonal IgM protein by immunofixation, Normal serum IgM level, Complete response of extramedullary disease, No splenomegaly or lymphadenopathy if present at baseline, Morphologically normal in bone marrow aspirate and biopsy, No symptoms and signs caused by macroglobulinmia.
- Very good partial remission (VGPR): Monoclonal IgM protein is detectable, > 90% reduction in serum IgM level from baseline, Complete response of extramedullary disease, No splenomegaly or lymphadenopathy if present at baseline, No new signs or symptoms of active disease.
- Partial response (PR): Monoclonal IgM protein is detectable, > 50% but < 90% reduction in serum IgM level from baseline, Reduction in lymphadenopathy/splenomegaly if present at baseline, No new signs or symptoms of active disease.
- Minor response (MR): Monoclonal IgM protein is detectable, ≥25% but <50% reduction in serum IgM level from baseline, No new signs or symptoms of active disease.
- Stable disease (SD): Monoclonal IgM protein is detectable, with < 25% reduction but increase also < 25% in serum IgM level from baseline, No progression in lymphadenopathy/splenomegaly, No new signs or symptoms of active disease.
- Progressive disease (PD): >25% increase in serum IgM level from nadir and/or progression in clinical manifestations attributable to disease.

Appendix 4: Study Design of Part I



Appendix 5: Flow Chart



Appendix 6 : Medications Caused QT/QTc Prolonged

Antiarrhythmics amiodarone disopyramide dofetilide flecainide ibutilide procainamide quinidine sotalol
Anticancer arsenic trioxide vandetanib
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