Clinical Study Protocol

Protocol Title:	**A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects with Relapsed/Refractory Waldenström's Macroglobulinemia (WM)**
Protocol Number:	**BGB-3111-210**
Study Phase:	**2**
Investigational Product:	**BGB-3111**
Indication:	**Relapsed/Refractory Waldenström's Macroglobulinemia**
Sponsor:	**BeiGene (Beijing) Co., Ltd** **No. 30 Science Park Road,** **Zhong-Guan-Cun Life Science Park** **Changping district, Beijing 102206** **China**
Coordinating Investigator:	[redacted] **China**
Sponsor Medical Monitor:	[redacted] **Email:** [redacted]
Original Protocol (Version 1.0):	**13 February 2017**
Amendment (Version 2.0):	**25 October 2017**
Amendment (Version 3.0):	**30 March 2018**

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SIGNATURES

PROTOCOL TITLE: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects with Relapsed/Refractory Waldenström's Macroglobulinemia (WM)

PROTOCOL NO: BGB-3111-210

DATE OF PROTOCOL: 30 March 2018, Version 3.0

[redacted]

3rd, Apr, 2018

Date

PROTOCOL AMENDMENT RATIONALE, VERSION 3.0

Protocol BGB-3111-210 (Version 3.0) is amended primarily for the following reasons:

- Corrected Study Assessments and Procedures Schedule: Remove targeted physical examination, align funduscopic examination with overall disease assessment frequency, and added optional plasma viscosity
- Revise the 5-point scale for assessment of causality text to match other protocols for BeiGene studies in China
- Clarify that patients with > Grade 1 toxicities per NCI-CTCAE from prior anti-cancer therapy, except for ANC, platelets, and hemoglobin, should be excluded from the study
- Clarify that for patients with HBV DNA < 1000 IU/mL, after enrollment, HBV DNA should be tested monthly **or every 3 cycles for patients receiving** ~~and~~ prophylactic anti-viral therapy ~~should be given~~ to prevent HBV reactivation

Changes were also made to the synopsis for consistency with the changes made within the protocol body.

In addition, administrative updates, editorial changes, and/or style and formatting revisions were made with the purpose of improving clarity and consistency throughout the document. **Bold** indicates added text; strikethrough indicates deleted text.

Substantial changes:

- Synopsis, Secondary Endpoints; Section 3.2; Section 10.1.2: Deleted the following text as shown as this was redundant: Resolution of treatment precipitating symptoms, defined as absence of symptoms at any point during study treatment, which triggered the initiation of study treatment as per the IWWM guidelines.
- Synopsis, Study Population; Section 5.2: Revised Exclusion Criterion #6 to clarify that patients with > Grade 1 toxicities per NCI-CTCAE from prior anti-cancer therapy, except for ANC, platelets, and hemoglobin, should be excluded from the study
- Synopsis, Study Population; Section 5.2; Section 7.1; Section 7.4.4.10: Revised text to clarify that for patients with HBV DNA < 1000 IU/mL, after enrollment, HBV DNA should be tested monthly **or every 3 cycles for patients receiving** ~~and~~ prophylactic anti-viral therapy ~~should be given~~ to prevent HBV reactivation
- Synopsis, Statistical Methods – Populations; Section 10.2.1; Revised text to clarify the analysis populations used in this study.
- Synopsis, Primary Efficacy Analysis; Section 10.2.5.1: Deleted text as shown to allow for flexibility: The primary efficacy analysis will be conducted when mature response rate data have been observed~~, estimated as no more than 12 months after the last subject received the first dose of study drug~~. Subsequent analyses will be performed when mature secondary efficacy endpoints are available.
- Section 5.2; Section 7.1: For patients that are HCV antibody +, added text as follows to match other sections of the protocol: HCV RNA < 15 IU/mL, monthly monitoring **or anti-viral treatment**
- Section 4.1: Revised text as shown for additional clarity: Subjects who have not progressed at the time of the final analysis and/or study closure, or subjects who had disease progression but are still benefitting from BGB-3111 treatment in the assessment of the investigator, will be considered to participate in the long-term extension study **if approved by sponsor.**

- Section 4.1, Section 6.7.1: Revised text for consistency with other BeiGene protocols: If a subject discontinues study drug due to reasons other than disease progression, efficacy evaluations will continue until subject exhibits first progression, ~~starts new anti-cancer therapy,~~ **withdrawal of consent**, death, **lost to follow-up**, or study termination **by sponsor**, whichever occurs first.
- Section 6.1: Revised study treatment text for consistency with other BGB-3111 protocols, and deleted Section 6.1.1 Food Effect Study as these study results are already stated in Section 1.6
- Section 6.5.1, Table 2: Corrected thrombocytopenia definition to Grade 4 for platelets < 25 x 10^9/L and significant bleeding
- Section 6.6.1: Clarified text: All concomitant medications taken during the study will be recorded in the eCRF with indication, **dosage** and dates of administration.
- Section 7.2 Study Assessments and Procedures Schedule; Section 7.3.1: Added separate row for funduscopic examination, with the following schedule to align with the frequency of overall disease assessment "**Funduscopic examination should be conducted in all subjects at screening and as clinically indicated. For abnormal results, the abnormal test should be repeated every 12 weeks for the first 48 weeks, then every 24 weeks (i.e, Cycles 4, 7, 10, 13, 19, 25, etc.), and at time of clinically indicated**."
- Section 7.2 Study Assessments and Procedures Schedule: Added as follows for feasibility at sites: Serum viscosity (optional)/**plasma viscosity (optional)**
- Section 7.2 Study Assessments and Procedures Schedule: Deleted text that is not applicable to this study: Windows: days allowed for reschedule of an entire visit due to logistic reasons (eg, Public Holidays). These are: ECOG, weight, vital signs, physical examination (including B symptoms), hematology, clinical chemistry, lipid panel, urinalysis, ~~T/B/NK cell count~~, serum Ig, concomitant medications, AEs/SAEs, pregnancy test, ~~pharmacokinetics~~, and study drug administration.
- Section 7.2 Study Assessments and Procedures Schedule; Section 7.4.2: Revised vital signs and physical examination text for consistency within the protocol and with the CRF: A complete ~~or targeted physical~~ examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified. Complete physical exam includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes /spleen, skin, oropharynx, extremities, and funduscopic examination, **as well as signs/symptoms with clinical relevance.** ~~Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms.~~
- Section 7.2 Study Assessments and Procedures Schedule: Revised footnote 11b to remove "blasts" for feasibility.
- Section 7.2 Study Assessments and Procedures Schedule; Section 7.3.3: Removed "required bone marrow involvement ≥10% (Gertz 2017)" for consistency with the inclusion/exclusion criteria.
- Section 7.2.2: Added text for clarity: Medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent **and during the screening phase**, and considered relevant for the subject's study eligibility will be collected and captured in the eCRF.
- Section 7.3: Revised text for consistency with other sections of the protocol: Serum immunoelectrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and

immunofixation studies will be performed Day 1 of every cycle for first 52 weeks (C1-C13) then every **3** ~~6~~ cycles (**C16, C19, C22,** ~~C19, C25, C31~~ etc.)

- Section 7.4.1: Revised text for clarity, and for consistency with other BeiGene protocols: **All adverse events, including SAEs, will be collected as described in Section 9.2.2.1.** ~~All AEs and SAEs, regardless of the relationship to the study drug, will be collected from the time of first dose of study drug.~~
- Section 7.4.4.8: Added text for consistency with Section 7.1 "If abnormal results present in screening, the urinary immunofixation should be repeated when CR is suspected"
- Section 9.1.2.1: Revised 5-point scale for assessment of causality text to match other protocols for BeiGene studies in China
- Section 10.2.3; Section 10.2.5.4: Deleted "disease stage" as a continuous variable, as this is not applicable to this indication
- Section 10.2.5.4: Deleted "Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data" as these data are not being collected in this study
- Section 10.3.2: Revised text for consistency with other BeiGene protocols: **A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first.** ~~A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or was worsening in severity from baseline (pretreatment)~~.
- Section 11.4: Deleted "Shipments of PK samples to assay laboratories" as PK was not included in this study.

Non-substantial changes:

- Changed the sponsor medical monitor to [redacted]
- Synopsis, Study Population: Added text to Inclusion Criteria #5 to match the Inclusion Criteria in Section 5.1
- Synopsis, Study Population: Added "of study drug" to Inclusion Criteria #7 and #8 for additional clarity.

SYNOPSIS

Name of Sponsor/Company:	**BeiGene (Beijing) Co., Ltd**
Name of Finished Product:	**BGB-3111 Capsules**
Name of Active Ingredient:	**BGB-3111**
Title of Study:	A Phase 2, Single-arm, Open-label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects with Relapsed/refractory Waldenström's Macroglobulinemia (WM)
Protocol No:	BGB-3111-210
Study Duration: Screening (up to 28 days); daily treatment until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination from sponsor, whichever occurs first; treatment (up to 3 years), safety follow up (30 days); survival follow-up (every 12 weeks) until data cutoff for final analysis.	Phase: 2

Objectives:

Primary:

- The primary objective of the study is to determine the efficacy of BGB-3111 in Chinese subjects with relapsed or refractory (R/R) Waldenström's Macroglobulinemia (WM) as measured by the major response rate (MRR) defined as the proportion of subjects who achieve complete response (CR) + very good partial response (VGPR) + partial response (PR), to be assessed by an independent review committee (IRC) according to an adaptation of the response criteria updated at the 6th International Workshop on Waldenström's Macroglobulinemia (IWWM) (Owen et al 2013; NCCN Guidance Insights, 2012).

Secondary:

- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by progression-free survival (PFS)
- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by overall response rate (ORR)
- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by duration of major response (DOMR)
- To characterize the clinical benefit of BGB-3111 in subjects with WM as determined by the frequency of resolution of treatment-precipitating symptoms
- To characterize the magnitude of improvement in bone marrow involvement with lymphoplasmacytoid lymphocytes in subjects with R/R WM treated with BGB-3111, as measured by the maximum decrease in percentage of lymphoplasmacytoid lymphocytes by bone marrow biopsy
- To determine the safety and tolerability of BGB-3111 in subjects with R/R WM as determined by the frequency and severity of AEs according to Common Terminology for Adverse Event (CTCAE) v4.03, and the rate of discontinuation of treatment, dose reduction and dose interruption of study drug due to AEs

Exploratory Objectives:

- To evaluate overall survival (OS) in subjects with WM

• To determine the complete response (CR) plus VGPR rate in MYD88^{MUT} WM • Evaluate drug resistance mechanisms through comparison of bone marrow aspiration at screening, and on relapse	
Methodology: This is an open-label, single-arm, multicenter Phase 2 study.	
Planned number of subjects:	Approximately 40 subjects will be enrolled.
Study Population	**Inclusion criteria:** 1. Clinical and definitive histologic diagnosis of WM (Gertz et al 2017), meeting at least one criterion for treatment according to consensus panel criteria from the Seventh International Workshop for Waldenström's Macroglobulinemia (IWWM) (Dimopoulos et al 2014) 2. WM pathology confirmation by central lab prior to study enrollment. Previous pathology report, concurrently with newly generated central lab report to be reviewed to support WM diagnosis 3. Men and women ≥ 18 years of age 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (see Appendix 6) 5. Previously treated with a minimum of 1 prior line of standard chemotherapy-containing regimen (with completion of ≥ 2 continuous treatment cycles) 6. Documented failure to achieve at least minor response or documented disease progression after response to the most recent treatment regimen. 7. Neutrophils ≥ 0.75 x 10^9/L independent of growth factor support within 7 days of first dose of study drug 8. Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of first dose of study drug 9. Hemoglobin ≥ 80g/L, independent of erythropoietin (EPO) support or transfusion within 7 days of first dose of study drug 10. Creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation (Cockcroft et al 1976) or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]) 11. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN) 12. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome) 13. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 x ULN. Patients with lupus anticoagulant or acquired von Willebrand disease due to WM may be enrolled after discussion with the medical monitor. 14. Echocardiogram (ECHO) must demonstrate left ventricular ejection fraction (LVEF) ≥ 50% (AHA 2016) 15. Subjects may be enrolled who relapse after autologous stem cell transplant if they are at least 6 months after transplant at screening. To be eligible after transplant, subjects should have no active

	related infections. 16. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control can be defined as abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for up to 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or use a barrier method where the female partner uses the effective forms of birth control noted above and must not donate sperm for at least 90 days after last dose of study drug. 17. Life expectancy of > 4 months 18. Able to provide written informed consent and can understand and comply with the requirements of the study **Exclusion criteria:** 1. Central nervous system (CNS) involvement by WM 2. Prior exposure to a Bruton's tyrosine kinase (BTK) inhibitor 3. Evidence of disease transformation 4. Prior corticosteroids given in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days. Prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, antineoplastic therapy with Chinese herbal medicine or antibody based therapies within 4 weeks of the start of study drug. 5. Major surgery within 4 weeks of randomization 6. Toxicity of > Grade 1 [NCI-CTCAE v4.03] from prior anti-cancer therapy (except for absolute neutrophil count [ANC] , platelets and hemoglobin. For ANC,platelets, and hemoglobin, please follow inclusion criteria #7 [neutrophils], #8 [platelets] and #9 [hemoglobin]) 7. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent 8. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification (see Appendix 8), or history of myocardial infarction within 6 months of screening 9. QTcF prolongation (defined as a QTc > 480 msecs based on Fridericia's formula) or other significant electrocardiogram (ECG) abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block 10. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

11. Active infection including infections requiring oral or intravenous anti-microbial therapy
12. Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR])

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody (+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA< 1000 IU/ml, After enrollment, check HBV DNA monthly or every 3 cycles for patients receiving prophylactic anti-viral therapy to prevent HBV reactivation	HBsAg (-) HBcAb (+)	HBV DNA ≥ 1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA< 15 IU/mL monitoring monthly or anti-viral treatment	Antibody (+)	HCV RNA ≥ 15 IU/mL

Abbreviation: HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HIV: human immunodeficiency virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

13. Pregnant or lactating women
14. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk
15. On medications which are strong CYP3A inhibitors or strong CYP3A inducers
16. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
17. Has received allogenic hematopoietic stem cell transplantation prior to enrollment

Test Product, Dose and Mode of Administration:	BGB-3111 160 mg twice a day (BID) (two 80 mg white to off-white opaque capsules) administered orally
Reference Therapy, Dose, and Mode of Administration:	Not applicable

Study Treatment:

BGB-3111 160 mg will be administered orally BID. Treatment with BGB-3111 may be continued for up to 3 years until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow up, or study termination by sponsor. At the time of final analysis, subjects who remain on treatment will be considered for participation in the extension study when eligible. A treatment cycle consists of 28 days.

The guidelines set forth in the following Table should be followed for dose interruption or modification of

BGB-3111 for hematologic and non-hematologic toxicity (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events; laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events).

Table 1 BGB-3111 Dose Reduction for Toxicity Occurrence

Toxicity Occurrence	Dose Level	BGB-3111 Dose Modification (starting dose 160 mg BID)
First	0 = starting dose	Restart at 160 mg BID
Second	-1 dose level	Restart at 80 mg BID
Third	-2 dose level	Restart at 80 mg QD
Fourth	Discontinue BGB-3111	Discontinue BGB-3111

Abbreviations: BID=twice a day; QD=once daily

Study drug may be held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the subject's best interest to restart study drug after more than 28 days, investigator need to discuss with sponsor and a written approval issued by the sponsor medical monitor after requested by investigator is needed before the restart of study drug.

Dose Reductions for Hematologic Toxicity

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

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

Dosing may be restarted at time of recovery of neutrophils ≥ $0.75x10^9$/L (growth factor support permitted) or platelet recovery to ≥ $50x10^9$/L, the dose will restart at full dose. If the same event reoccurs, subjects will restart at one dose level lower. Maximum 2 dose reductions are allowed. Subjects with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention will be discontinued from study treatment. Asymptomatic lymphocytosis should not be regarded as an AE, and these subjects should continue taking study drug (Cheson et al 2012).

Dose Reductions for Non-Hematologic Toxicity

For non-hematological toxicities ≥ Grade 3, other than hypertension adequately controlled with oral medication or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events), suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1 or baseline, and then restarted at original dose level. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -1. If the event recurs at ≥ Grade 3 at level -1, drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -2. If the event recurs at ≥ Grade 3 the subject will be discontinued from study treatment. For subjects experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled the study drug may be restarted at either the original dose or dose level-1, per discretion of the treating investigator. BGB-3111 should be permanently discontinued for any intracranial hemorrhage.

Concomitant Therapy and Clinical Practice:

Tumor Lysis Syndrome (TLS) has not been reported with BGB-3111 treatment, but has been reported rarely with ibrutinib. Subjects with high tumor burden should be monitored closely and prophylactic measures, including hydration, diuretics, allopurinol, may be instituted per institutional standards.

Prohibited Concomitant Therapy

During study treatment, subjects are prohibited from receiving any anticancer therapy, including but not limited to chemotherapy, immunotherapy, corticosteroids (at dosages equivalent to > 10 mg/day of prednisone), experimental therapy, radiotherapy, and Chinese herbal medications used for anti-cancer therapy. Corticosteroid courses (at dosages equivalent to prednisone > 10 mg/day) of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition. Bisphosphonates that have been in steady use for over 3 months are permitted.

Drugs known to prolong the QT/QTc interval are prohibited

In accordance with the Food and Drug Administration (FDA) Guidance for Industry (FDA 2005): Drugs known to prolong QT interval should be avoided. If a patient requires treatment with any of these medications on study, and a non-QT prolonging alternative medication is not available, the medical monitor must be notified. Upon approval by the medical monitor, treatment with study drug should be withheld immediately and recommenced at least 5 half-lives following the last use of the QT prolonging medication. A list of drugs with QTc prolongation potential is provided in Appendix 2.

Concomitant Use of Cytochrome (CYP) Inhibiting/Inducing Drugs

Information about clinical drug interactions with BGB-3111 is not available. Based on available non-clinical metabolism data, BGB-3111 is primarily metabolized by CYP3A. Avoid concomitant administration of BGB-3111 with strong CYP3A inhibitors or strong CYP3A inducers (refer to Appendix 4 for a list of these medications). Grapefruit juice and Seville oranges should be avoided, as they may affect the metabolism of BGB-3111. For short-term use (treatment for ≤ 7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting BGB-3111 therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations.

BGB-3111 is a moderate inhibitor of the human isoenzymes CYP2C8, CYP2C9, and CYP2C19. Drugs that are primarily metabolized by these isoenzymes should be used with caution when administering BGB-3111, with monitoring of drug concentrations as appropriate (refer to Appendix 5 for examples of these medications). Study treatment for BGB-3111 should be held for 3 to 7 days pre-post surgery depending upon the type of surgery and the risk of bleeding, if a subject is to undergo surgery during Treatment Phase.

Criteria for Evaluation:

Response will be evaluated based on independent review committee (IRC) according to an adaptation of the response criteria for WM evaluation (see Appendix 3). Serum immunoglobulin (IgG, IgM, IgA, κ, λ) and β2-microglobulin will be measured at screening, on Day 1 of every cycle for the first 52 weeks, then every 3 cycles thereafter. Assessment by computed tomography (CT) scan will occur at screening and every 12 weeks during the first 48 weeks, and then every 24 weeks until disease progression. Bone marrow will be assessed by aspirate and biopsy at screening, every 24 weeks, at time of suspected CR and as clinically indicated. If at any time disease progression is suspected, clinical examination with radiological confirmation should be performed without necessity to wait for next evaluation time point.

An IRC will be established for response evaluation, and details of which will be written in the IRC charter. Response assessments will be compared to predose IgM level (baseline). For the evaluation of progressive disease (PD), IgM will be compared to IgM nadir.

The safety of this study will be monitored by safety monitoring committee (SMC), its organization and detailed execution will be written in the SMC charter. The SMC will evaluate safety data, and advise

accordingly. Subjects will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI-CTCAE v. 4.03]) and serious adverse events (SAEs). Subjects who, at time of progression, have an ongoing AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the subject is lost to follow-up, or the subject starts a different anti-tumor therapy.

In the case of major toxicity or efficacy concerns, the SMC can recommend modifying the trial conduct.

Primary Endpoint:

The primary endpoint of the study is the MRR, defined as the proportion of subjects who achieve CR + VGPR + PR, to be assessed by an IRC according to an adaptation of the response criteria updated at the 6th International Workshop on Waldenström's Macroglobulinemia (IWWM) (Owen et al 2013; NCCN Guidance Insights, 2012).

Secondary Endpoints

Efficacy (using response assessment as determined by IRC):

- PFS: defined as time from first dose of BGB-3111 until first documentation of progression (by IWWM criteria) or death, whichever comes first.
- ORR: defined as the proportion of subjects with a minor, partial, very good partial, and complete response.
- DOMR: defined as the time from the date that the major response criteria are first met to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.
- Resolution of treatment precipitating symptoms, defined as absence of symptoms at any point during study treatment.
- Anti-lymphoma effect is defined as any reduction during the course of study treatment in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly by computed tomography (CT) scan. Lymphadenopathy is defined as any node with longest diameter (LDi) > 1.5 cm and splenomegaly is defined as vertical spleen length > 13 cm.

Safety:

To evaluate the safety and tolerability of BGB-3111, as defined by:

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

Exploratory Endpoints:

- OS defined as the time from the date of the first dose of BGB-3111 until date of death from any cause
- CR plus VGPR rates in subjects with $MYD88^{MUT}$ WM
- Identification of potential drug resistance biomarkers and mechanisms: paired bone marrow aspiration (at screening and at relapse) will be used to identify potential biomarkers and mechanisms.

Statistical Methods:

Populations:

The Safety Population (SP) includes all subjects who received at least one dose of BGB-3111; this population will be used for all safety analyses. The Revised Safety Population (RSP) includes subjects with pathologically confirmed WM among those in the SP; this population will be used for all efficacy analyses.

The Per-Protocol Population (PP) includes subjects who received any dose of BGB-3111 and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. The PP population will be used for select efficacy analyses.

Primary Efficacy Analysis:

The primary endpoint is MRR, defined as the proportion of subjects who achieve CR + VGPR + PR, as determined by IRC review. In this population, MRR in the historical control is assumed to be approximately 30% based on recent trials. The MRR in this study is estimated as 60%, which is deemed a clinically meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: major RR=30%
Ha: major RR ≥30%

A binomial exact test will be performed for hypothesis testing in the Safety Population. If the obtained 1-sided p-value is less than or equal to 0.025, it will be concluded that the single agent BGB-3111 statistically significantly increases MRR compared with historical control. Therefore, the superiority of single agent BGB-3111 will be demonstrated.

A two-sided Clopper-Pearson 95% confidence interval (CI) of MRR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed. Subsequent analyses will be performed when mature secondary efficacy endpoints are available.

Secondary Efficacy Analysis:

ORR as determined by IRC review. Overall response rate, defined as the proportion of subjects who achieves CR, VGPR, PR, and minor response (MR) according to an adaptation of the response criteria updated at the 6th Workshop on Waldenström's Macroglobulinemia (Owen et al 2013; NCCN Guidance Insights, 2012), will be estimated in the Safety population. Clopper-Pearson 95% CI will be constructed for calculating exact binomial intervals for ORR.

Best overall response (BOR) is defined as the best response recorded from the start of BGB-3111 until data cut or start of new anti-neoplastic treatment. Subjects with no post-baseline response assessment (due to whatever reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, VGPR, PR, MR, stable disease [SD], and PD) will be presented.

PFS is 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.

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

Median PFS, if estimable, will be estimated using the Kaplan-Meier method. Its 2-sided 95% CIs, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. Kaplan-Meier estimates of PFS will be plotted over time. The PFS at 6 months, defined as the percentage of subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula.

The DOMR will be analyzed similarly as PFS.

Resolution of cytopenias, organomegaly, neuropathy, and maximum decrease in percentage of lymphoplasmacytoid lymphocytes in bone marrow will be summarized descriptively at each visit.

Exploratory efficacy Analyses:

OS will be analyzed using Kaplan-Meier method described above. Kaplan-Meier estimates of OS will be plotted over time.

CR plus VGPR rates will be determined in patients with $MYD88^{MUT}$ as the proportion of patients who achieve VGPR or CR.

Safety Analysis:

Safety will be assessed by monitoring and recording of all AEs including all CTCAE v4.03 grades (both increasing and decreasing severity), regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs and performance of physical examinations (PEs). Descriptive statistics will be used to analyze all safety data in the Safety Population.

Sample Size:

Approximately 40 subjects will be enrolled. The sample size of 40 subjects was based on the precision of a MRR estimate and the power of the comparison to the historical rate, assuming a MRR of 60% in the study as compared to 30% in the historical control. Using a binomial exact text, the power is >0.969 with 40 subjects to demonstrate statistical significance at a 1-sided alpha of 0.025 under above assumption.

For an observed MRR of 60%, the 95% exact CI is (43.3%, 75.1%) with a sample size of 40 subjects.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antigen-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AEs	adverse events
ALCs	absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AV	atrioventricular
BCR	B-cell receptor
BID	twice a day
BOR	best overall response
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood counts
CFDA	Chinese Food and Drug Administration
CDE	Center for Drug Evaluation
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
Clad-R	cladribine plus rituximab
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report reform
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	CXC-chemokine receptor 4
CYP	cytochrome

CYP3A	cytochrome P450, family 3, subfamily A
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOMR	duration of major response
DRC	dexamethasone, rituximab, and cyclophosphamide
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMD	extramedullary disease
EOT	end of treatment
EPO	erythropoietin
FDA	Food and Drug Administration
FL	follicular lymphoma
FRK	fyn-related kinase
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDL	high density lipoprotein
HDPE	high density polyethylene
HER	human epidermal growth factor receptor
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Institutional Review Committee

ITK	interleukin-2-inducible T cell kinase
IWWM	International Workshop for Waldenström's Macroglobulinemia
JAK3	Janus kinase 3
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LDi	longest diameter
LDL	low density lipoprotein
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
MYD88	myeloid differentiation primary response gene 88
MRR	major response rate
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	Non-Hodgkin Lymphomas
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PEs	physical examinations
PFS	progression-free survival
PLCβ2	phospholipase C-beta-2
PK	pharmacokinetics
PP	per-protocol population
PR	partial response
PT	prothrombin time
PT	preferred term
QD	once daily
QT	interval between the beginning of the QRS complex to the end of the T wave
RBC	red blood cell

R-CHOP	rituximab- cyclophosphamide, doxorubicin, vincristine, and prednisone
R-FC	rituximab plus fludarabine plus cyclophosphamide
RR	response rate
R/R	relapsed or refractory
SAEs	serious adverse events
SAP	Statistical Analysis Plan
SD	stable disease
SLL	small lymphocytic lymphoma
SMC	Safety monitoring committee
SOC	system organ class
SOP	standard operating procedures
SP	Safety Population
TEAEs	treatment emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TLS	Tumor Lysis Syndrome
TMD-8	transmembrane domain 8
ULN	upper limit of normal
VGPR	very good partial response
WBCs	white blood cells
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia
X	to be performed

1. INTRODUCTION

1.1 Current Status of Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia (WM) is a generally indolent and relatively rare B-cell lymphoplasmacytic lymphoma, characterized by bone marrow infiltration with monoclonal immunoglobulin M (IgM) protein secretory lymphoplasmacytic cells. The incidence is 5-8 per million population, less than 2% of all Non-Hodgkin Lymphomas (NHLs), with about 1000-1500 new patients diagnosed in the United States annually. Incidence increases with age with a median age at diagnosis of 70 years for Caucasians, and slightly lower in other ethnic groups, the incidence being 0.41 in Caucasians, 0.18 in African American, and 0.21 in other ethnic group including Asians (Wang H et al 2012), with a male to female preponderance, and an incidence higher in Caucasians than Africans or Asians (Gertz et al 2000; Gertz et al 2015). GLOBOCAN 2015 reports yearly and 5-year incidence of NHLs to be $3.1/10^5$ and $7.6/10^5$ respectively in China, much lower than in the United States ($14.7/10^5$ and $80.3/10^5$) or Europe ($8.8/10^5$ and $45/10^5$), and counting WM to be 2% of all NHLs, that results in 522 new cases per year in China.

Two mutations are common in WM, 90% of patients have an activating mutation in the myeloid differentiation primary response gene 88 (MYD88) gene, ($MYD88^{L265P}$), which triggers downstream IRAK-and Bruton's tyrosine kinase (BTK) mediated NF-κB signaling (Treon et al 2012) and is seen in the vast majority of patients. A second set of mutations with prognostic significance is found at CXC-chemokine receptor 4 (CXCR4), the receptor for SDF-1a, which are either frameshift or nonsense mutations, are similar to those seen in the immunodeficiency syndrome WHIM (warts, hypogammaglobulinemia, infections and myelokathexis), and also lead to constitutive activation. Either or both of these mutations can be found in WM patients and lead to different clinical pictures, outcomes, and response to therapy with best response to the BTK inhibitor ibrutinib found in $MYD88^{MUT}$ $CXCR4^{WT}$ (Treon et al 2014).

Bone marrow involvement by lymphoplasmacytic cells is reported in 80% of patients, Waldenström's cellular infiltrate can be diffuse, nodular or mixed, although none of the patterns have any prognostic significance. The tumor cells strongly express CD19, CD20, CD22, as well as surface immunoglobulin.

According to the International Prognostic Scoring System for WM, patients are stratified into low, intermediate, and high risk groups with respective 5-year survival rates of 87%, 68%, and 36%. The scoring system scores adverse co-variates including: age > 65 years, IgM > 70 g/L, β2-microglobulin > 3 mg/L, hemoglobin (Hgb) ≤ 11.5 g/dL, platelets ≤ 100 $x10^9$/l; one adverse co-variate is low risk, 2 is intermediate risk, and if greater than 2 adverse co-variates, the patient is in the high risk group. (Morel et al 2009).

About 75% of asymptomatic WM patients will require therapy within 15 years of follow-up, with a median time to initiation of therapy of over 7 years; a lower Hgb, extensive bone marrow infiltration, serum M-spike, and β2-microgobulin levels are significant predictors of an eventual need for therapy. (Gertz et al 2015). Indications for treatment as per the International Workshop for Waldenström's Macroglobulinemia (IWWM)-7 consensus meeting are either clinical symptoms or laboratory findings. Clinical indications include the combination of fever, night sweats, weight loss and fatigue, hyperviscosity syndrome, bulky/symptomatic lymphadenopathy, significant hepatomegaly or splenomegaly, other symptomatic organomegaly, or peripheral neuropathy. Additional indications for therapy include symptomatic cryoglobulinemia, cold agglutinemia, moderate to severe hemolytic anemia, amyloidosis, renal impairment, or significant anemia/thrombocytopenia due to marrow replacement.

Current treatment strategies for symptomatic WM patients include single agent rituximab (35% and 20% major response rate (MRR) in 1st and 2nd line therapy respectively), the addition of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) increases the MRR to 50%-60% (Jacobson and Freedman 2013). Bendamustine, dexamethasone plus rituximab has shown activity with similar overall response rates to rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but with prolonged progression free survival and better tolerability (Rummel et al 2013). Dexamethasone, Rituximab, and cyclophosphamide (DRC), bendamustine plus rituximab (BR), and proteasome inhibitor-based therapy such as bortezomib (25-27% MRR in 1st line, and 2nd line respectively) chlorambucil (36% MRR in 1st line), or carfilzomib in combination with rituximab. In patients with symptomatic viscosity or those with high IgM levels who are at risk of disease flare prior to rituximab treatment, plasmapheresis should be performed. Other chemotherapeutic regimens may include rituximab plus fludarabine (45% MRR in 1st line) plus cyclophosphamide (R-FC), and cladribine plus rituximab (Clad-R). For select WM patients, stem cell transplantation is an option in the salvage setting (Leblond et al 2016; Owen et al 2014). Novel treatment agents for WM may include immunomodulatory agents like lenalidomide, the mammalian target of rapamycin inhibitor everolimus, as well as the serine/threonine kinase inhibitor enzastaurin and the histone deacetylase inhibitor panobinostat.

Recently, the BTK inhibitor ibrutinib was approved for refractory WM, having demonstrated a 90% single agent response rate with a time-to-progression of 9.6 months. Patients whose WM harbored the MYD88^{L256P} CXCR4^{WT} mutations had 100% response rate, compared to 85.7% in MYD88^{L256P} CXCR4^{WHIM} mutations, and only 71.4% response if both genes were wild type (Treon et al 2015). However, none of these drugs have been approved by the Chinese Center for Drug Evaluation (CDE) for use in WM treatment. In addition, even if these drugs have good efficacy in WM, these patients will still relapse, and with the significant toxicity incurred from toxic agents, a more potent and effective, yet less toxic, easy to administer treatment would cater to such an unmet medical need.

Treatment-related toxic effects of ibrutinib which were Grade 2 or higher included neutropenia (in 22% of the patients) and thrombocytopenia (in 14%), which were more common in heavily pretreated patients; post procedural bleeding (in 3%); epistaxis associated with the use of fish-oil supplements (in 3%); and atrial fibrillation associated with a history of arrhythmia (5%) (Treon et al 2015).

Treatment with BTK inhibitors can incur transient increase in lymphocytes in over 70%-97% of chronic lymphocytic leukemia (CLL) and 40%-70% of mantle cell lymphoma (MCL) patients. Absolute lymphocyte counts (ALCs) generally peak around 4-8 weeks, and take 4-8 months to return to baseline. This lymphocytosis is generally asymptomatic, requires no medical management, and does not signify disease progression, therefore treatment with the B cell inhibitors should be continued (Cheson et al 2012, Chang et al 2013; Woyach et al 2014）.

1.2 BGB-3111

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

1.3 BGB-3111 Non-Clinical Data

BGB-3111 inhibits BTK with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomolar (nM) in biochemical assays. Cellular assays confirmed that BGB-3111 inhibited B-cell receptor (BCR) aggregation-triggered BTK autophosphorylation, and blocked downstream phospholipase C-beta-2 (PLCβ2) signaling in MCL cell lines. BGB-3111 potently and selectively inhibited cellular growth of several MCL cell lines (REC-1, Mino, and JeKo-1) and activated B-cell (ABC) type of diffuse large B-cell lymphoma (DLBCL) cell line transmembrane domain 8 (TMD-8), with IC_{50}s from 0.36 nM to 20 nM, while inactive in many other hematologic cancer cell lines. In vivo studies showed that BGB-3111 induced dose-dependent anti-tumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. BGB-3111 was more selective than ibrutinib for inhibition of kinase activity of BTK vs. EGFR, Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), fyn-related kinase (FRK), human epidermal growth factor receptor (HER)2, HER4, ITK, JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and TEC. Cellular assays also confirmed that BGB-3111 is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antigen-dependent cell-mediated cytotoxicity (ADCC). BGB-3111 was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced ADCC, consistent with BGB-3111

being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays, thus preventing the potential for antagonism with rituximab that has been seen preclinically with other BTK inhibitors.

1.4 BGB-3111 Global Phase 1 Clinical Trial

The first-in-human study with BGB-3111, which was designed to look at safety and pharmacokinetics (PK) in subjects with B-cell lymphoid malignancies, started in Australia in August 2014. As of October 3, 2016, a total of 171 subjects have been enrolled and 128 subjects remained on study. The maximum tolerated dose was not reached. As of the data cutoff, 104/171 patients (61%) had experienced at least one treatment-emergent adverse event (TEAE) assessed by the investigator as related to study treatment, including 40/61 patients (66%) with CLL/ small lymphocytic lymphoma (SLL), 33/63 (52%) with NHL, and 31/47 (66%) with WM. As of October 3, 2016, 58/171 patients (34%) had experienced a serious adverse event (SAE), including 15/61 patients (25%) with CLL/SLL, 29/63 (46%) with NHL, and 14/47 (30%) with WM. The most common SAEs overall were pneumonia (4%) and pleural effusion (2%).

1.5 BGB-3111 China Phase 1 Clinical Trial

The investigational new drug (IND) package for BGB-3111 was approved by the Chinese Food and Drug Administration (CFDA) in February of 2016. The Phase 1 clinical trial, designated BGB-3111-1002, enrolled its first subject in July 2016. Three subjects each were enrolled on two dose schedules 320 mg once daily (QD) or 160 mg twice a day (BID). After observation over a 28-day period for dose-limiting toxicity (DLT), none were reported, and 7 more subjects were enrolled in each arm. As of October 27, 2016， a total of 21 subjects treated on 2 dose schedules, 16 male, and 5 female, age range from 34 to 67 years of age, 9 CLL/SLL, 6 follicular lymphoma, 2 subjects each of MCL, marginal zone lymphoma, and WM. As of October 27, 2016, all subjects have passed DLT evaluation period, 11 subjects received 160 mg BID, 10 subjects received 320 mg QD, no DLT observed. AEs include the following Grade 4 events: 4 subjects with neutropenia, 1 with thrombocytopenia, 1 with QT prolongation, 1 with leucocytosis, and 1 with upper respiratory tract infection. So far, 5 subjects have completed their first evaluation; all attained partial response (PR), including 3 with CLL, 1 with WM, and 1 with follicular lymphoma (FL).

1.6 BGB-3111 Pharmacokinetics and Pharmacodynamics

In the first-in-human, Phase 1 study (BGB-3111-AU-003), the PK of BGB-3111 was linear between 40 mg and 320 mg daily administered orally (BGB-3111 Investigator's Brochure [IB]). The absorption of BGB-3111 is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 4 hours at 320 mg daily. Results from a food effect study showed that BGB-3111 exposure was not altered by a high-fat breakfast, and mean area under the plasma concentration time curve (AUC) and maximum observed plasma concentration

(C_{max}) were increased by 12% and 51%, respectively, with a standard breakfast when compared to fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg administered daily in the ongoing Phase 1 study, and was not associated with any new safety findings, therefore BGB-3111 can be administered with or without food.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all subjects in the study, while occupancy in lymph node tissue was assessed only at 160 mg BID and 320 mg QD. At both schedules, full BTK occupancy was observed at trough exposure periods, suggesting that sustained target occupancy could be achieved in disease-originating tissues. Activity has been observed across indications at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive experience at the 160 mg BID and 320 mg QD; both schedules show a high level of activity without compromise of the tolerability profile as compared to lower doses of BGB-3111. Therefore, the dose of 320 mg QD is selected as the recommended Phase 2 dose based on sustained target occupancy, high rates of objective response in multiple histologies, and a favorable safety and tolerability profile.

1.7 Use of BGB-3111 in Waldenström's Macroglobulinemia

BTK, a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, is a critical component of the B-cell receptor (BCR) signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib, the first-in-class FDA-approved BTK inhibitor, has demonstrated promising anti-tumor activity in WM.

BGB-3111 is a potent, specific and irreversible BTK inhibitor. The data generated in preclinical studies using biochemical, cell based and animal studies suggest that BGB-3111 could offer significant patient benefit in inhibiting tumor growth in WM, and as BGB-3111 was shown to be more selective than ibrutinib for inhibition of BTK, may have a favorable side effect profile, allowing for higher and more prolonged exposure to drug, allowing for more sustained BTK inhibition, potentially enhancing clinical efficacy.

As of the cut-off date, of the subjects fully evaluable for safety and efficacy in the phase I studies, 15 subjects had a diagnosis of WM with a median follow-up of 4.7 months. Among the 15 subjects with WM, 13 (87%) achieved a major response. Of these 13 subjects, 4 patients had a > 90% reduction in IgM from baseline, thus meeting IgM criteria for very good partial response (VGPR). To date, no cases of disease progression following a treatment response have been observed. Refer to the BGB-3111 IB for more detailed information.

For these reasons, we believe that a single-arm Phase 2 open-label study of the BTK inhibitor BGB-3111, in subjects with WM requiring treatment is indicated. Historical MRR will be set as 30%.

2. OBJECTIVES

2.1 Primary Objective

- The primary objective of the study is to determine the efficacy of BGB-3111 in Chinese subjects with R/R WM as measured by the MRR defined as the proportion of subjects who achieves CR + VGPR + PR, to be assessed by an IRC according to an adaptation of the response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012).

2.2 Secondary Objectives

- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by PFS
- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by ORR
- To determine the efficacy of BGB-3111 in subjects with R/R WM as measured by DOMR
- To characterize the clinical benefit of BGB-3111 in subjects with WM as determined by the frequency of resolution of treatment-precipitating symptoms
- To characterize the magnitude of improvement in bone marrow involvement with lymphoplasmacytoid lymphocytes in subjects with R/R WM treated with BGB-3111, as measured by the maximum decrease in percentage of lymphoplasmacytoid lymphocytes by bone marrow biopsy
- To determine the safety and tolerability of BGB-3111 in subjects with R/R WM as determined by the frequency and severity of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and the rate of discontinuation of treatment, dose reduction and dose interruption of study drug due to AEs

2.3 Exploratory Objective

- To evaluate OS in subjects with WM
- To determine the CR plus VGPR rates in $MYD88^{MUT}$ WM
- Evaluate drug resistance mechanisms through comparison of bone marrow aspiration at screening, and on relapse

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study is the MRR, defined as the proportion of subjects who achieve CR + VGPR + PR, to be assessed by an IRC according to an adaptation of the response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012).

3.2 Secondary Endpoints

Efficacy (using response assessment as determined by IRC):

- PFS: defined as time from first dose of BGB-3111 until first documentation of progression (by IWWM criteria) or death, whichever comes first.
- ORR: defined as the proportion of subjects with a minor, partial, very good partial, and complete response.
- DOMR: defined as the time from the date that the major response criteria are first met to the date that PD is objectively documented or death, whichever occurs first.
- Resolution of treatment precipitating symptoms, defined as absence of symptoms at any point during study treatment.
- Anti-lymphoma effect is defined as any reduction during the course of study treatment in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly by CT scan. Lymphadenopathy is defined as any node with longest diameter (LDi) > 1.5 cm and splenomegaly is defined as vertical spleen length > 13 cm.

Safety:

To evaluate the safety and tolerability of BGB-3111, as defined by:

- The incidence and severity of TEAEs, SAEs and treatment-related AEs according to CTCAE v4.03
- The incidence, severity, and causation of AEs leading to study drug discontinuation, dose reduction and dose interruption

3.3 Exploratory Endpoints

- OS defined as the time from the date of the first dose of BGB-3111 until date of death from any cause
- CR plus VGPR rates in subjects with $MYD88^{MUT}$ WM

- Identification of potential drug resistance biomarkers and mechanisms: paired bone marrow aspiration (at screening and at relapse) will be used to identify potential biomarkers and mechanisms.

3.4 The Choice of Endpoints

Efficacy: the choice of endpoints has been determined by the impact of BTK inhibitors, such as ibrutinib, on the pathophysiology of WM. The purpose of this clinical trial is to demonstrate the benefit/risk ratio of BGB-3111. All these endpoints have been evaluated in previous WM clinical trials, such that the data obtained from this clinical trial can easily be compared to historical results.

Safety and Tolerability: tyrosine kinase inhibitors can have an impact on QT interval prolongation, even though in the first 57 patients enrolled in Australia, this has not been reported, but this is still a potential issue to be observed. Off target inhibition of platelet function with resultant bleeding is another issue to be closely scrutinized. In addition, there will be close follow up of Grade 3 and Grade 4 hematological toxicity and infection.

4. STUDY DESIGN

4.1 Summary of Study Design

This is a single-arm, open-label, multi-center Phase 2 study in subjects with WM requiring therapy using the consensus panel criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012). The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase. Subjects who have not progressed at the time of the final analysis and/or study closure, or subjects who had disease progression but are still benefitting from BGB-3111 treatment in the assessment of the investigator, will be considered to participate in the long-term extension study if approved by sponsor. The study schema is presented in Figure 1.

Approximately 40 subjects will be enrolled. The primary efficacy analysis will be conducted at up to 12 months after the last subject receives the first dose of study drug. Tumor response will be assessed by independent review according to response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012). IgM level will be measured at screening, on Day 1 of every cycle for the first 52 weeks, then every 3 cycles thereafter. Assessment by CT scan will occur every 12 weeks during the first 48 weeks, and then every 24 weeks until disease progression. Bone marrow will be assessed by aspirate and biopsy at screening, every 24 weeks, at time of suspected CR and as clinically indicated.

All subjects will be followed for AEs for 30 ± 7 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations. Please refer to Table 3 for details on screening procedures. Screening evaluations can be repeated within the screening period.

Treatment phase: Subjects will receive the first dose of BGB-3111 at Cycle 1 Day 1. All subjects will be treated with 160 mg, administered orally, BID, about 12± 2 hours apart, and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. A treatment cycle is 28 days.

Per the Owen criteria, an assignment of PD only requires 2 IgM measurements ≥25% from nadir and total increase in IgM must be ≥ 500mg/dL from nadir while on treatment. In other studies there have been cases where a subject nadirs early on in treatment, then the IgM levels increase for a 1 to 2 months, then come back down and stay down, together with reduction or stabilization of extramedullary disease (EMD). Therefore, after discussion between the investigator and the medical monitor, subjects will be allowed to remain on study if their investigators judge that the subjects are clinically benefiting from continued treatment with BGB-3111 even if the subjects meet the criteria for PD based only on changes in their IgM levels. These subjects will no longer be included in efficacy assessments after a determination of PD but will be followed for safety.

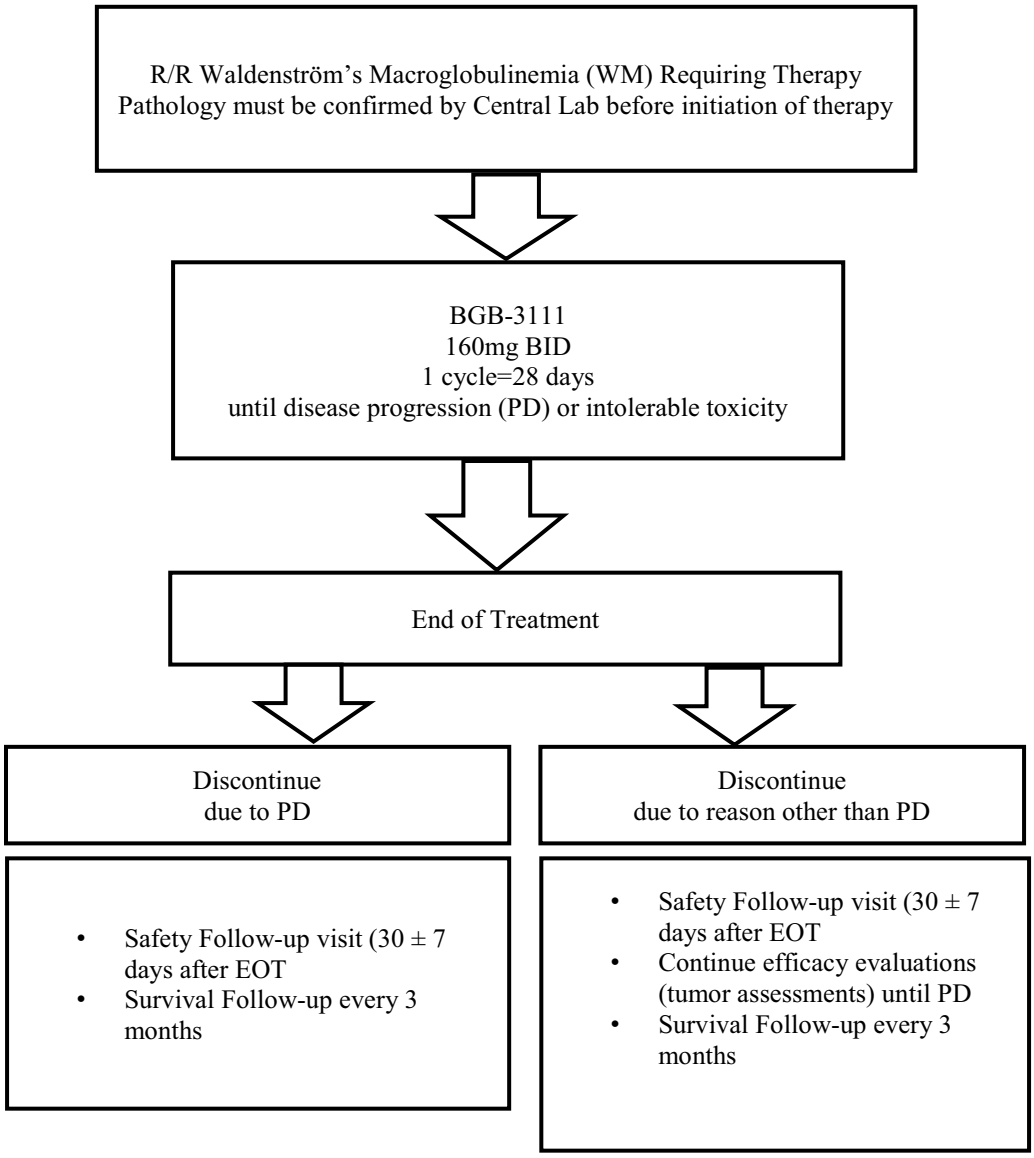
Follow-up phase: Subjects will return 30 ± 7 days after the last dose of study drug for safety follow-up visit(s). Assessments to be performed are presented in Table 3. Efficacy evaluations will continue until documented disease progression. If a subject discontinues study drug due to reasons

other than disease progression, efficacy evaluations will continue until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination by sponsor, whichever occurs first.

Survival Follow-up phase: After attending the last visit, the subject/guardian will be contacted by telephone every 3 months for follow up, and this will continue up until the patient withdraws informed consent, lost to follow up, death, or final data cut off.

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

Figure 1 Schema for Study BGB-3111-210



5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Clinical and definitive histologic diagnosis of WM (Gertz et al 2017), meeting at least one criterion for treatment according to consensus panel criteria from the Seventh IWWM (Dimopoulos et al 2014)
2. WM pathology confirmation by central lab prior to study enrollment. Previous pathology report, concurrently with newly generated central lab report to be reviewed to support WM diagnosis
3. Men and women ≥ 18 years of age
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 6)
5. Previously treated with a minimum of 1 prior line of standard chemotherapy-containing regimen (with completion of ≥ 2 continuous treatment cycles)
6. Documented failure to achieve at least minor response or documented disease progression after response to the most recent treatment regimen.
7. Neutrophils ≥ 0.75 x 10^9/L independent of growth factor support within 7 days of first dose of study drug
8. Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of first dose of study drug
9. Hemoglobin ≥ 80g/L, independent of erythropoietin (EPO) support or transfusion within 7 days of first dose of study drug
10. Creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation (Cockcroft and Gault 1976) or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD])
11. AST and ALT ≤ 3.0 x ULN
12. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome)
13. INR ≤ 1.5 and APTT ≤ 1.5 x ULN. Patients with lupus anticoagulant or acquired von Willebrand disease due to WM may be enrolled after discussion with the medical monitor
14. ECHO must demonstrate left ventricular ejection fraction (LVEF) ≥ 50% (AHA 2016)

15. Subjects may be enrolled who relapse after autologous stem cell transplant if they are at least 6 months after transplant at screening. To be eligible after transplant, subjects should have no active related infections.

16. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control can be defined as abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for up to 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or use a barrier method where the female partner uses the effective forms of birth control noted above and must not donate sperm for at least 90 days after last dose of study drug.

17. Life expectancy of > 4 months

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

5.2 Exclusion Criteria

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

1. Central nervous system (CNS) involvement by WM
2. Prior exposure to a BTK inhibitor
3. Evidence of disease transformation
4. Prior corticosteroids given in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days. Prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, antineoplastic therapy with Chinese herbal medicine or antibody based therapies within 4 weeks of the start of study drug.
5. Major surgery within 4 weeks of randomization
6. Toxicity of ≥ Grade 1 [NCI-CTCAE v4.03] from prior anti-cancer therapy (except for absolute neutrophil count [ANC], platelets, and hemoglobin. For ANC, platelets, and hemoglobin, please follow inclusion criteria #7 [neutrophils], #8 [platelets], and #9 [hemoglobin])
7. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent
8. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac

disease as defined by the New York Heart Association (NYHA) Functional Classification (see Appendix 8), or history of myocardial infarction within 6 months of screening

9. QTcF prolongation (defined as a QTc > 480 msecs based on Fridericia's formula) or other significant ECG abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block
10. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
11. Active infection including infections requiring oral or intravenous anti-microbial therapy
12. Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR])

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody (+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-), HBcAb (+)	HBV DNA < 1000 IU/mL, After enrollment, check HBV DNA monthly or every 3 cycles for patients receiving prophylactic anti-viral therapy to prevent HBV reactivation	HBsAg (-), HBcAb (+)	HBV DNA ≥ 1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA < 15 IU/mL, monthly monitoring or anti-viral treatment	Antibody (+)	HCV RNA ≥ 15 IU/mL

Abbreviation: HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HIV: human immunodeficiency virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

13. Pregnant or lactating women
14. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk
15. On medications which are strong CYP3A inhibitors or strong CYP3A inducers
16. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
17. Has received allogenic hematopoietic stem cell transplantation prior to enrollment

6. STUDY TREATMENTS

6.1 Study Treatment

BGB-3111 will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take BGB-3111 with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. BGB-3111 capsules should not be opened, broken, or chewed at any time.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

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 space to enter the subject number, content and quantity of BGB-3111, protocol number, batch number, administration instructions, storage conditions, and cautions.

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

6.2.2 Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Study drug must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may dispense the study drug to enrolled subjects. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel. The study drug must be kept at the condition as specified on the labels, or according to the latest version of the IB.

6.2.3 Compliance and Accountability

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

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

6.2.4 Disposal and Destruction

After completion of the study, and following final drug inventory reconciliation by the monitor, all unused BGB-3111 will be inventoried and packaged for return shipment by the investigator and/or designated site personnel. The inventoried supplies will be returned to the sponsor or destroyed on site or depot, after receiving written sponsor approval.

6.3 Subject Numbering and Treatment Assignment

6.3.1 Subject Numbering

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned when the subject is screened or enrolled in the study. Subject will be assigned in chronological order starting with the lowest number. Once a subject number has been assigned to a subject, it cannot be reassigned to any other subject.

6.3.2 Treatment Assignment

All subjects in the study will receive BGB-3111.

6.3.3 Treatment Blinding

This is an open-label study.

6.4 Dosage and Administration

BGB-3111 will be dispensed on Day 1 of each cycle in the first 13 cycles of the first year (every 4 weeks), and then Day 1 of every 3 cycles (every 12 weeks starting from Cycle 13) by the study center personnel. Subjects will be provided with an adequate supply of study drug for self-administration at home. The investigator should instruct the subject to take the study drug exactly as prescribed. Subjects will be requested to bring their unused medication including empty packaging to the center at each visit. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

Subjects will be instructed to take 160 mg (two 80 mg capsules) BID, orally with a glass of water. BGB-3111 will be taken daily from Cycle 1 Day 1 until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow up, or the study is terminated by the sponsor for final analysis.

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

6.5 Dose Interruption and Modification

The guidelines set forth in Table 1 should be followed for dose interruption or modification of BGB-3111 for hematologic (Section 6.5.1), non-hematologic toxicities (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events; laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) (Section 6.5.2).

Table 1 BGB-3111 Dose Reduction for Toxicity Occurrence

Toxicity Occurrence	Dose Level	BGB-3111 Dose Modification (starting from 160 mg BID)
First	0 = starting dose	Restart at 160 mg BID
Second	-1 dose level	Restart at 80 mg BID
Third	-2 dose level	Restart at 80 mg QD
Fourth	Discontinue BGB-3111	Discontinue BGB-3111

Abbreviations: BID= twice a day; QD=once daily

Study drug may be held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the subject's best interest to restart study drug after more than 28 days, investigator need to discuss with sponsor and a written approval issued by the sponsor medical monitor after requested by investigator is needed before the restart of study drug.

6.5.1 Dose Reductions for Hematologic Toxicity

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

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

Dosing may be restarted at time of recovery of neutrophils ≥ $0.75x10^9$/L (growth factor support permitted) or platelet recovery to ≥ $50x10^9$/L, the dose will restart at full dose. If the same event reoccurs, subjects will restart at one dose level lower. Maximum 2 dose reductions are allowed.

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

For fever associated with neutropenia, take medical history, perform physical examinations (PEs), and the relevant imaging, and blood, body fluid cultures to ascertain cause of infection, and administer anti-infective therapy as per hospital guidelines. Growth factor use should be considered as per investigator judgement.

Table 2 Dose Reductions for Hematologic Toxicity

Adverse Event	Severity and Duration	Time to Restart	Dose Modification
Absolute neutrophil count decreased	CTCAE Grade 4 (<0.5x10^9/L) lasting >10 days	Recover to ANC >0.75×10^9/L	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
Platelet count decreased	CTCAE Grade 4 (<25x10^9/L) lasting >10 days	Recover to Platelet > 50×10^9/L	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
Febrile neutropenia	CTCAE Grade 3 (ANC<1x10^9/L & single T>38.3°C, or sustained T>38°C >1hr)	Recover to ANC> 0.75×10^9/L and body temperature recovery	Restart at 160mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
	CTCAE Grade 4 (Life-threatening consequences; urgent intervention indicated)	Recover to ANC> 0.75×10^9/L and body temperature recovery	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID → 80 mg QD (Table 1)
Thrombocytopenia accompanied by bleeding	CTCAE Grade 3 (Platelets 25-50 x10^9/L) and significant bleeding	Discontinuation	NA
	CTCAE Grade 4 (Platelets <25 x10^9/L) and significant bleeding	Discontinuation	NA

Abbreviations: ANC = absolute neutrophil count; BID= twice a day; CTCAE= Common Terminology Criteria for Adverse Events; NA= not applicable; QD= once daily

Asymptomatic lymphocytosis should not be regarded as an AE, and these subjects should continue taking study drug (Cheson et al 2012).

6.5.2 Dose Reductions for Non-Hematologic Toxicity

For non-hematological toxicities ≥ Grade 3, other than hypertension adequately controlled with oral medication or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events), suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1 or baseline, and then restarted at original dose level. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -1. If the event recurs at ≥ Grade 3 at level -1, drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -2. If the event recurs at ≥ Grade 3 the subject will be discontinued from study treatment. For subjects experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled the study drug may be restarted at either the original dose or dose level-1, per discretion of the treating investigator. BGB-3111 should be permanently discontinued for any intracranial hemorrhage.

6.6 Concomitant Medications and Non-Drug Therapies

6.6.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication, dosage and dates of administration.

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-WM indications
    - Patients should not receive treatment with systemic corticosteroids other than intermittently to control or prevent infusion reactions, or for short durations (at dosages equivalent to prednisone >10 mg/day for <2 weeks,) to treat non-WM-related conditions (eg, to treat a flare of chronic obstructive pulmonary disease)
- Therapy to reduce symptoms per standard of care and institutional guidelines
- Bisphosphonates that have been in steady use for over 3 months are permitted

6.6.1.1 Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS) has not been reported with BGB-3111 treatment, but has been reported rarely with ibrutinib. Subjects with high tumor burden should be monitored closely and prophylactic measures, including hydration, diuretics, allopurinol, may be instituted per institutional standards.

6.6.2 Prohibited Medications

During study treatment, subjects are prohibited from receiving any anticancer therapy, including but not limited to chemotherapy, immunotherapy, corticosteroids (at dosages equivalent to > 10 mg/day of prednisone), experimental therapy, radiotherapy, and Chinese herbal medications used for anti-cancer therapy. Corticosteroid courses (at dosages equivalent to prednisone > 10 mg/day) of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition. Bisphosphonates that have been in steady use for over 3 months are permitted.

Drugs known to prolong the QT/QTc interval should be avoided 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 (FDA 2005). If a patient requires treatment with any of these medications on study, and a non-QT prolonging alternative medication is not available, the medical monitor must be notified. Upon approval by the medical monitor, treatment with study drug should be withheld immediately and recommenced at least 5 half-lives following the last use of the QT prolonging medication. A list of drugs with QTc prolongation potential is provided in Appendix 2.

Potent CYP3A inducers and inhibitors. The primary metabolic pathway for BGB-3111 involves the CYP3A isoform. The compounds/substances presented in Appendix 4 are either strong CYP3A4 inhibitors or inducers which are prohibited in the current study. For short-term use (treatment for ≤ 7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting BGB-3111 therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations.

6.6.3 Medications to be used with Caution

BGB-3111 is a moderate inhibitor of human CYP isoenzyme CYP2C8 (IC_{50} = 4.03 μM), CYP2C9 (IC_{50} = 5.69 μM), and CYP2C19 (IC_{50} = 7.58 μM). Although unlikely to reach the drug concentration that could cause significant inhibition of these CYP enzymes in clinic based on the human PK prediction, investigators should be aware that BGB-3111 has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C8, CYP2C9, and CYP2C19. Examples of these medications include, but are not limited to the following, and these should be used cautiously with the monitoring of drug concentrations where appropriate. (Please refer Appendix 5).

6.6.4 Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment for BGB-3111 should be held for 3 to 7 days pre-post surgery depending upon the type of surgery and the risk of bleeding, if a subject is to undergo surgery during Treatment Phase.

6.7 Discontinuation of Treatment and Premature Withdrawal

When the study drug is permanently discontinued regardless of reason, the subject will have an End of Treatment (EOT) visit within 7 days of stopping study drug. A visit should be scheduled as soon as possible, at which time all of the assessments listed for the EOT visit will be performed (see Table 3). The reason for discontinuation from treatment will be recorded on eCRF.

6.7.1 Discontinuation of Treatment

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

- Death
- Disease progression
- Unacceptable and unmanageable toxicity attributed to BGB-3111
- Pregnancy
- Subject misses > 28 consecutive days of dosing.
- Subject withdrew consent, permitted at any time during the trial.

All subjects who discontinue study drug will have a safety follow-up visit approximately 30±7 days after the last dose of study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the treatment. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment will only be performed if the subject had an ongoing laboratory abnormality at the previous visit which the investigator considered to be related to study drug. If the subject is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the subject or guardian to collect this information.

Subjects who are discontinued from study drug for any reason (i.e. AE or administrative reasons etc.) other than disease progression should not be considered withdrawn from the study. They will continue to be followed for efficacy evaluations per schedule outlined in Table 3 until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them by telephone to determine the subject's disease status and survival.

6.7.2 Premature Withdrawal

Subjects will be withdrawn from the study for one of the following reasons:

- Study Termination by sponsor
- Significant non-compliance of the patient
- Lost to follow up

If the subject is lost to follow up, investigators should try best to contact with the patient to make sure the reason of withdrawal. The information should be recorded in the source document and eCRF.

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

7. STUDY ASSESSMENTS

7.1 Study Flow and Visit Schedule

The study specific assessments and procedures are shown in Table 3.

Table 3 Study Assessments and Procedures Schedule for Study BGB-3111-210

	Pre-treatment	**Treatment** **All cycles are 28 days (4 weeks) in duration**				**End of Study Assessments**		
	Screening [1]	**Cycle 1**	**Cycle 2**	**Cycle 3 to Cycle 13 (every 4 weeks)**	**Cycle 16, Cycle 19, Cycle 22… (every 12 weeks)**	**EOT**	**Safety Follow-up Visit**	**Survival Follow-up (every 12 weeks)**
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (±4 days)**	**Day 1 (±4 days)**	**Day 1 (±7 days)**	**(Within 7 days after stopping treatment)**	**30 days after EOT (±7 days)**	
Visit	0	1	2	3, 4, 5, etc.…				
Informed consent	X [2]							
Inclusion/exclusion criteria	X [3]							
Demography	X [4]							
Medical/surgical history/current medical conditions	X [5]							
Diagnosis and extent of cancer	X [6]							
Prior antineoplastic therapy	X							
12-lead ECG [7]	X					X		
ECHO/ multigated acquisition scan (MUGA) [8]	X							
Lipid panel	X [9]							
ECOG performance status	X	X	X	X	X (every cycle)	X	X	
Height (in cm)	X							

Weight (in kg)	X	X	X	X	X (every cycle)	X	X	
Vital signs and physical examination (including assessment of B symptoms and liver and spleen enlargement,)	X [10a]	X	X	X	X (every cycle)	X	X	
Funduscopic examination	X [10b]	For abnormal results, the abnormal test should be repeated every 12 weeks for the first 48 weeks, then every 24 weeks (i.e, Cycles 4, 7, 10, 13, 19, 25, etc.), and at time of clinically indicated.						
Hematology [11]	X	X	X	X	X (every cycle)	X		
Chemistry [11]	X	X	X	X	X (every cycle)	X		
Coagulation [11]	X	X						
Urinalysis (macroscopic; microscopic if required) [11]	X	X	X	X	X (every cycle)	X		
Cold agglutinins (optional) [11]	X	For any abnormal result, the abnormal test should be repeated every cycle for the first 52 weeks, then every 3 cycles, and at time of suspected CR.						
Cryoglubulin (optional) [11]	X	For any abnormal result, the abnormal test should be repeated every cycle for the first 52weeks, then every 3 cycles, and at time of suspected CR.						
Anti-MAG (myelin associated glycoprotein) (optional) [11]	X	For any abnormal result, the abnormal test should be repeated every cycle for the first 52weeks, then every 3 cycles, and at time of suspected CR.						
Serum viscosity (optional) /plasma viscosity (optional)[11]	X	For any abnormal result, the abnormal test should be repeated every cycle for the first 52weeks, then every 3 cycles, and at time of suspected CR.						

Hepatitis B/C testing [11]	X	Subjects with HBcAb positive and HBV DNA < 1000 IU/ml: after enrollment, HBV DNA should be tested monthly or every 3 cycles for patients receiving prophylactic anti-viral therapy to prevent HBV reactivation. Subjects with HCV antibody positive but negative for HCV RNA <15 IU/ml must undergo monthly HCV RNA monitoring at each cycle or anti-viral treatment.						
Pregnancy test (if applicable)	X [11]	X	X	X	X	X		
Study drug administration [12]		X	X	X	X			
CT scan with contrast of neck/chest/abdomen and pelvis (or MRI)[13]	X	Every 12 weeks during the first 48 weeks, then every 24 weeks (Cycle 4, Cycle 7, Cycle 10, Cycle 13 and Cycle 19 etc.)						
Brain CT/MRI scan[13]	Clinical indicated							
Concomitant medications	Throughout							
AEs/SAEs	Throughout							
Antineoplastic therapies since discontinuation of study drug							X	X
Survival follow-up [14]								X
Following examinations will be performed in central laboratory								
Urinary immunoglobulins, urinary β2-microglobulin, and urinary immunofixation [15]	X	For any abnormal result at screening, the abnormal test should be repeated at time of suspected CR.						
Serum immunoglobulins and serum β2-microglobulin [16]	X	Every cycle during the first 52 weeks (C1-C13), then every 3 cycles (C16, C19, C22, …) and at time of CR.						
Serum immunoelectropheresis and serum immunofixation [17]	X	Every cycle during the first 52 weeks (C1-C13), then every 3 cycles (C16, C19, C22…) and at time of CR.						

Bone marrow biopsy/aspiration [18]	X	Every 24 weeks (C7, C13, C19, C25), at time of CR and clinical indicated; Optional bone marrow aspiration will be collected in subjects with progressive disease.			

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

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

Assessments scheduled on Cycle 1 Day 1 should be performed prior to the administration of the first dose of BGB-3111. Screening blood and urine tests performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

1. Screening evaluations will be performed and completed within 28 days prior to the first dose of BGB-3111. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to Cycle 1 Day 1.
2. Written informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
3. The investigator will review and ensure that the subject meets all of the inclusion and none of the exclusion criteria.
4. Demography includes gender, date of birth (or age).
5. Relevant medical history (ie. previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility, and current medical conditions.
6. Diagnosis and extent of cancer. Other background information including history of disease and current disease status, staging, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.
7. Perform a 12-lead ECG in triplicate at screening and EOT. Subjects should be in the semi-recumbent or supine position.
8. An ECHO will be performed at screening. An ECHO performed within 30 days of first dose can be substituted.
9. Lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides performed at screening only.
10. Vital signs and physical examination:
    a. A complete examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified. Complete physical exam includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes /spleen, skin, oropharynx, extremities, and funduscopic examination, as well as signs/symptoms with clinical relevance. Clinical suspicion of disease progression at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats. Symptoms of WM, if present, should be assessed for improvement, worsening, or resolution.

b. Funduscopic examination: Funduscopic examination should be conducted in all subjects at screening and as clinically indicated. For abnormal results at screening and discerned as related to WM by the investigators, the abnormal test should be repeated every 12 weeks for the first 48 weeks, then every 24 weeks (ie., Cycles 4, 7, 10, 13, 19, 25 etc.), and at time of clinically indicated.

11. Laboratory assessments include the following:

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

    b. Hematology, including red blood cell (RBC) count, hemoglobin, hematocrit, reticulocyte count, white blood cell (WBC) count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils,) and platelet count. In the event of neutropenia (absolute neutrophil count < 750/mm^3) or thrombocytopenia (platelets of less than 50,000/mm^3), these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2 or baseline (ANC ≥ 750/mm^3).

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

    d. Coagulation profile will be performed at screening and Cycle 1 Day 1, and includes prothrombin time (PT), INR, and aPTT.

    e. Cold agglutinins; Cryoglobulin; Anti-MAG (myelin associated glycoprotein) and serum viscosity will be performed at screening (optional). If there are abnormal findings for any of these laboratory assessments at screening, follow-up is required every cycle (every 4 weeks) for the first 52 weeks, then every 3 cycles (every 12 weeks) starting on Cycle 16 (C16, C19, C22, etc.) and at time of suspected CR. Once these labs have normalized, they should be repeated every 3 cycles and at time of suspected CR.

    f. Hepatitis B/C serologic markers and viral load will be tested. The hepatitis B testing includes hepatitis B virus (HBV) deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb). The hepatitis C testing includes hepatitis C virus (HCV) ribonucleic acid (RNA) by PCR.

    g. Urinalysis will be performed. Urine microscopy will be performed if urinalysis is abnormal. Urinalysis includes pH, glucose, and protein. If urine protein is ≥2+, a 24-hour urine for total protein will be obtained and evaluated.

    h. 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.

12. Subjects will receive BGB-3111 at a dosage of 160 mg (two - 80 mg white to off-white opaque capsules) orally BID. BGB-3111 will be administered on a 28-day cycle and will continue for until disease progression, unacceptable toxicity, death, withdrawal of consent, end of study, or discontinuation from the study for any reason. All subjects will have an end of treatment (EOT) visit within 7 days after stopping study drug. All subjects will have a follow-up visit 30 ± 7 days after the last dose of the study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.

13. CT scans must encompass neck, chest, abdomen, and pelvis and include intravenous contrast. A brain scan is required if clinically indicated. In all case, an MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo contrast CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study. Tumor assessment by CT or scan will occur at screening and every 12 weeks ± 1week during the first 48 weeks, and then every 24 weeks ± 1week until disease progression or end of study, whichever comes first. Unscheduled response assessments may be performed based on physical examination or laboratory findings, at the discretion of the investigator.
14. Survival information will be collected via telephone call every 3 months after the subject's last visit until after the subject's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
15. Urinary immunoglobulins (quantitation of κ, λ), urinary β2-microglobulin, and urinary immunofixation (IgG, IgA, IgM, κ, λ) will be performed at screening in central laboratory. For any abnormal result at screening, the abnormal test should be repeated at time of suspected CR.
16. Serum immunoglobulin (IgG, IgM, IgA, κ, λ) and β2-microglobulin will be measured at screening and Day 1 of every cycle for the first 52 weeks (C1-C13), then every 3 cycles thereafter during the treatment period (C16, C19, C22, …) in central laboratory.
17. Serum immunoelectropheresis will be performed at screening and Day 1 of every cycle for the first 52 weeks (C1-C13), then every 3 cycles thereafter during the treatment period (C16, C19, C22…) in central laboratory.
18. A bone marrow examination (biopsy and aspiration) must be performed at screening for all subjects . Bone marrow examination (biopsy and aspiration) will be performed every 24 weeks, at time of suspected CR, and as clinically indicated. Please refer to Appendix 7 for the detailed bone marrow examination tests. Bone marrow specimen will be sent to central laboratory to check MYD88 and CXCR4 mutations status. Optional bone marrow aspiration will be collected in subjects with progressive disease to study the mechanism and biomarkers of drug resistance.

7.2 Subject Demographics/Other Baseline Characteristics

7.2.1 Demography

Demographic data will include gender, date of birth (or age).

7.2.2 Medical History

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

7.2.3 Other Baseline Characteristics

Other background information including history of disease and current disease status, staging, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.

Not all patients with a diagnosis of WM need immediate therapy. Criteria for the initiation of therapy (Seventh IWWM) (Dimopoulos et al 2014) are presented in Table 4. Subjects who do not fulfill the criteria in Table 4 at screening and in whom only laboratory evidence may indicate a possible development of symptomatic disease (such as a minor decrease in hemoglobin level, but >10 g/dL, or mild increases in IgM or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient) are not eligible for the study.

Table 4 Clinical Indications for Initiation of Therapy

Clinical indications for initiation of therapy
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy due to WM
Laboratory indications for initiation of therapy
Symptomatic cryoglobulinemia
Cold agglutinin anemia

Immune hemolytic anemia and/or thrombocytopenia
Nephropathy related to WM
Amyloidosis related to WM
Hemoglobin ≤10 g/dL
Platelet count <100 × 10^9/L

Abbreviations: WM= Waldenström's Macroglobulinemia
Castillo et al, 2016

Information will also be collected regarding child-bearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, and ECG). For further details on eligibility assessments, please see Table 3.

7.3 Efficacy

Response will be evaluated using the consensus panel criteria updated at the 6th IWWM (Owen et al 2013). Please refer to Appendix 3 for categorical response definitions. Response assessments will be compared to predose IgM level (baseline). For the evaluation of progressive disease (PD), IgM will be compared to IgM nadir.

Clinical evaluation and tumor assessments will be performed as indicated in Table 3, based on PEs, laboratory evaluations (Serum immunoelectrophoresis with quantification of immunoglobulins [IgM, IgG, IgA] and immunofixation studies], radiological assessment, symptom assessment, and bone marrow biopsy and aspiration.

At screening (within 28 days of the first dose), a bone marrow biopsy/aspirate, serum immunoelectrophoresis and immunofixation studies, quantitative immunoglobulin (IgM, IgG, IgA), and β2-microglobulin. CT scanning of the neck, chest, abdomen, and pelvis will be performed. Bone marrow samples must be performed during screening with specimen sent for biomarkers as described in Section 7.5.

Serum immunoelectrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies will be performed Day 1 of every cycle for first 52 weeks (C1-C13) then every 3 cycles (C16, C19, C22, etc.). β2-microglobulin will also be performed every cycle for the first 52 weeks (C1-C13), then every 3 cycles thereafter during the treatment period.

In the event either cold agglutinins, cryoglobulin, anti-MAG (myelin associated glycoprotein), or serum viscosity are found to be abnormal at screening, then the abnormal laboratory test will be repeated every cycle for the first 52 weeks, then every 3 cycles, and at time of suspected CR. Once

these labs have normalized, they should be repeated every 3 cycles and at the time of a suspected CR. For subjects with previous biopsy positive for amyloidosis, a fat pad biopsy or biopsy of other relevant tissue will be collected at the time of suspected CR by IgM response.

For the first 48 weeks of study drug treatment, radiological tumor assessment will be performed every 12 weeks ± 1 week, then every 24 weeks ± 1 week thereafter. A CT scan will also be repeated to confirm CR.

7.3.1 Physical Examination

At every clinical visit, PEs should be performed with assessment of B symptoms (>10% unintentional weight loss, fever, and night sweats), and presence/absence of hepatosplenomegaly. Symptoms of WM, if present, should be assessed for improvement, worsening, or resolution. Funduscopic examination: Funduscopic examination should be conducted in all subjects at screening and as clinically indicated. For abnormal results at screening and discerned as related to WM by the investigators, the abnormal test should be repeated every 12 weeks for the first 48 weeks, then every 24 weeks (i.e, Cycles 4, 7, 10, 13, 19, 25, etc.), and at time of clinically indicated.

7.3.2 Radiological Tumor Assessment

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

All subjects must have contrast CT scan of neck, chest, abdomen, and pelvis. Brain imaging will only be performed as clinically indicated on study if there is suspicion of CNS involvement.

The contrast CT scan will occur at screening and every 12 weeks for the first 48 weeks (± 7 days), and at CR if the subject has absence of serum monoclonal IgM protein and normal serum IgM level, thereafter, every 24 weeks (± 7 days) until documented disease progression according to consensus panel criteria updated at the 6th IWWM (Appendix 3).

A magnetic resonance imaging (MRI) may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study.

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

7.3.3 Bone Marrow Assessment

A bone marrow examination (biopsy and aspiration) must be performed at screening for all subjects. Bone marrow examination (biopsy and aspiration) will be performed every 24 weeks, at time of

suspected CR, and as clinically indicated. Please refer to Appendix 7 for the detailed bone marrow examination tests.

Bone marrow specimen will be sent to central laboratory and MYD88 and CXCR4 mutation analysis will be performed. Optional bone marrow aspiration will be collected in subjects with PD to study the mechanism and biomarkers of drug resistance.

7.3.4 Missed Evaluations

If a subject missed an evaluation, it should be rescheduled as close to the original time as possible，unless the next evaluation time is coming up, and in the investigators opinion, the extra evaluation is unnecessary and not safe.

7.4 Safety

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 3.

7.4.1 Adverse Events

All adverse events, including SAEs, will be collected as described in Section 9.2.2.1. All subjects will be followed for safety 30 ± 7 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 9.1. In addition, SAEs will be reported after informed consent has been signed but prior to the administration of the study drug, and, after the 30 days after the last dose of study drug, the investigator should report any SAEs that are believed to be related to prior study drug treatment. Important additional requirement for reporting SAEs are explained in Section 9.2. Secondary malignancies will be recorded as AEs and should be reported to

the sponsor. Transformation of WM to large cell lymphoma (Richters transformation) is considered as PD and should not be recorded in the eCRF as an AE.

7.4.1.1 Asymptomatic Drug Induced Lymphocytosis

In this protocol, study drug induced lymphocytosis is defined as ≥ 50% increase over baseline, and the absolute value is ≥ 5,000/μL, concurrently, a disease parameter (including lymphadenopathy, hepatosplenomegaly, hemoglobin, or platelet count) significantly improves.

As a physiological effect of BTK inhibitors, treatment-related lymphocytosis is an expected common occurrence and will not be reported as an AE. Study medication should not be interrupted in the event of treatment-related lymphocytosis.

7.4.2 Physical Examination, Vital Signs, Height, and Weight

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

A complete PE includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities and funduscopic examination, as well as signs/symptoms with clinical relevance.

7.4.3 ECOG Performance Status

ECOG performance status will be assessed at the Screening Visit, Day 1 of each treatment cycle, and at EOT Visit. Appendix 6 will be used to assess performance status.

7.4.4 Laboratory Evaluations

Laboratory assessments should be performed at a local certified laboratory and central lab. Clinical chemistry, hematology, coagulation, urinalysis, serum immunoglobulin, and β2-microglobulin will be performed at the time points specified in Table 3, and may also be performed as medically indicated. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and urine tests should be performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

7.4.4.1 Hematology

Hematology includes hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils. In the event of neutropenia (ANC < 0.75 x 10^9/L) or thrombocytopenia (platelets < 50 x 10^9/L), these assessments will be conducted as frequently as the

investigator feels it necessary and until toxicity resolves to ≤ Grade 2 or baseline (ANC ≥ 0.75 x 10^9/L; platelets ≥ 50 x 10^9/L).

7.4.4.2 Clinical Chemistry

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

7.4.4.3 Serum Lipid Profile

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

7.4.4.4 Coagulation

The coagulation profile includes prothrombin time (PT), which will also be reported as INR and activated partial thromboplastin time (APTT). The coagulation profile will be performed at screening and on Cycle 1 Day 1.

7.4.4.5 Urinalysis

Urinalysis will be performed. Urine microscopy will be performed if urinalysis is abnormal. Urinalysis includes pH, glucose, and protein. If urine protein is ≥2+, a 24 hour urine for total protein and a random urine for total protein will be obtained and evaluated.

7.4.4.6 Serum Immunoglobulin and β2-microglobulin

Serum immunoglobulin (IgG, IgM, IgA, κ, λ) and β2-microglobulin will be measured at screening and on Day 1 of every cycle for the first 52 weeks (C1-C13), then every 3 cycles thereafter (C16, C19, C22…) during the treatment period in the central laboratory. If subjects discontinue study drug due to reasons other than PD, serum immunoglobulin will continue to be followed every 12 weeks until subject exhibits disease progression, starts with new anti-cancer therapy, death, or study termination, whichever occurs first. It is recommended that sequential response assessments for individual subjects are performed in the same laboratory using the same methodology.

7.4.4.7 Serum Immunoelectrophoresis

Serum immunoelectrophoresis and serum immunofixation will be performed at screening and Day 1 of every cycle for the first 52 weeks (C1-C13), then every 3 cycles thereafter during the treatment period in central laboratory. If subjects discontinue study drug due to reasons other than PD, serum immunoelectrophoresis and serum immunofixation will continue to be followed every 12 weeks

until subject exhibits disease progression, starts with new anti-cancer therapy, death, or study termination, whichever occurs first.

7.4.4.8 Urinary Immunoglobulins, Urinary β2-microglobulin, and Urinary Immunofixation

Urinary immunoglobulins (quantitation of κ, λ), urinary β2-microglobulin, and urinary immunofixation (IgG, IgA, IgM, κ, λ) will be performed at screening in central laboratory. If abnormal results present in screening, the urinary immunofixation should be repeated when CR is suspected.

7.4.4.9 Pregnancy Test

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

7.4.4.10 Hepatitis B and C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb) as well as HBV DNA by PCR if the subject is negative for HBsAg, but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or HBV DNA ≥ 1000 IU/mL or detectable level of HCV RNA (≥ 15 IU/mL) are not eligible. Subjects who are HBsAg negative and HBcAb positive must initiate antiviral therapy during study treatment and undergo monthly HBV DNA screening by PCR. Resumption of study drug in subjects whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B and the medical monitor.

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

Table 5 shows how the results for HBV/HCV, and HBV/HCV testing at screening relate to inclusion and exclusion criteria.

Table 5 Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by

Polymerase Chain Reaction [PCR])

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody (+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA < 1000 IU/mL, After enrollment, check HBV DNA monthly or every 3 cycles for patients receiving prophylactic anti-viral therapy to prevent HBV reactivation.	HBsAg (-) HBcAb (+)	HBV DNA > 1000 IU/mL
HCV	Antibody (-)			
	Antibody (+)	HCV RNA < 15 IU/mL, monthly monitoring or anti-viral treatment.	Antibody (+)	HCV RNA > 15 IU/mL

Abbreviations: HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HIV: human immunodeficiency virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

7.4.5 Electrocardiogram

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

7.5 Biomarkers

The mutational status of the MYD88 and CXCR4 genes has been shown to predict responsiveness of the BTK inhibitor ibrutinib in WM (Treon et al 2015). All subjects will have mutation analysis of MYD88 and CXCR4 performed on bone marrow samples.

7.6 Appropriateness of Measurements

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

8. DATA HANDLING AND QUALITY ASSURANCE

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

8.1 Data Collection

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

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

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

8.2 Data Management/Coding

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

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

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

8.3 Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory

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

9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

9.1 Adverse Events

9.1.1 Definitions and Reporting

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

Examples of an AE include:

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

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

9.1.2 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE v4.03).

Toxicities that are not specified in the NCI CTCAE v4.03 will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities as described in Section 9.2.

9.1.2.1 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the IB in the determination of his/her assessment.

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

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

- Definitely related: There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (when necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment
- Probably related: This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study treatment that: There is reasonable temporal relationship; the occurrence of AE could not be explained by the subject's medical history, concurrent medical condition, or other the subject's signs or symptoms; the positive of de- challenge result; the positive of re-challenge result.
- Possibly related: There is some evidence to suggest a causal relationship (e.g., the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (e.g., the subject's clinical condition, other concomitant AEs).
- Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the AE.
- Unrelated: An AE will be considered "not related" to the use of the product if any of the following tests are met:
    - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the AE occurred either before, or too long after administration of the product for it to be considered product-related);
    - A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident);
    - A clearly more likely alternative explanation for the AE is present (e.g., typical adverse
    - Reaction to a concomitant drug and/or typical disease-related AE).

9.1.2.2 Follow-Up of Adverse Events and Serious Adverse Events

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

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

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations that may be indicated to elucidate the nature and/or causality of the AE

or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

9.1.3 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood counts (CBC), coagulation, or urinalysis) or other abnormal assessment (eg, ECGs, X-rays, vital signs) findings that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 9.1.1) or an SAE (as defined in Section 9.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The abnormal laboratory findings should be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, need dose interruption or discontinuation, or are clinically significant in the opinion of the investigator.

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

9.2 Serious Adverse Events

9.2.1 Definitions

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

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

- Results in disability/incapacity

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

- Is a congenital anomaly/birth defect

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

Disease progression should not be reported as an AE/SAE, but symptoms meeting the definition of, and associated with, disease progression should be reported.

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

9.2.2.1 Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study treatment of BGB-3111. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

9.2.2.2 Eliciting Adverse Events

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

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

9.2.3 Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.2.3.1 Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

9.2.3.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (eg, clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report, if applicable). However, if a subject initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE

should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

9.2.3.3 Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, it should be recorded as a new AE on the eCRF (and a stop date should be recorded in the previous AE).

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

9.2.3.4 Disease Progression

Disease progression is expected in this study population, and the term “disease progression” should not be reported as an AE term. When disease progression is identified, the AE that identifies the disease progression should be reported as the AE term. For instance, a subject with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as “pleural effusion” instead of “disease progression” or “metastasis to lungs.” If a subject has a seizure that is determined to be associated with a brain metastasis, the term “seizure” should be recorded as the AE instead of “disease progression” or “brain metastasis.” If a subject experiences multiorgan failure due to disease progression, the term “multi-organ failure” should be reported as the AE instead of “disease progression.” Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data. They should not be reported as SAEs. A patient death not solely due to disease progression as assessed by the investigator should be reported as an SAE immediately, regardless of relationship to study drug.

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

9.2.3.5 Death

When recording a death as a SAE outcome, the SAE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “unexplained death”.

9.3 Prompt Reporting of Serious Adverse Events

9.3.1 Time Frames for Submitting Serious Adverse Events

All SAE will be reported promptly to the sponsor or designee as described in Table 6 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 6 Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

9.3.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE (Section 9.6) has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.3.1. The SAE report form will always be completed as thoroughly as possible with all available details of the SAE, signed by the investigator and forwarded to the sponsor within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the SAE and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.2.1.

Facsimile transmission of the SAE report form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone or email is acceptable, with a copy of the SAE report form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE report form within the time frames outlined in Section 9.3.1.

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

9.3.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAE to the sponsor in accordance with the procedures detailed in Section 9.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical

investigation. Prompt notification of the appropriate project contact by the investigator for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

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

9.4 Pregnancy Reporting

If a female subject or the partner of a male subject becomes pregnant while receiving investigational therapy or within 90 days for BGB-3111 after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE, as described in Section 9.1 and Section 9.2 and will be followed as described in Section 9.1.2.2.

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

9.5 Post-study Adverse Event

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, defined in Section 9.2.2.1.

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

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

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

To determine the reporting requirements for individual SAE, the sponsor will assess the expectedness of the SAE using the current version BGB-3111 IB.

9.7 Safety Monitoring Committee

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

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

The study will set up a Safety Monitoring Committee (SMC). The SMC charter will define the organization’s members and procedures. The SMC will monitor safety data according to the SMC charter periodically throughout the study. This early safety review will occur 3 months after enrollment of the 25th subject or at 6 months after the first subject is enrolled, whichever comes first. No recruitment stop is planned for this interim safety review. In the case of major toxicity or efficacy concerns, the SMC can, according to the SMC charter, make recommendations to modify the trial conduct.

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

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

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

10.1 Primary, Secondary and Exploratory Study Endpoints

10.1.1 Primary Endpoint

The primary endpoint of the study is the MRR, defined as CR + VGPR + PR, to be assessed by an IRC according to an adaptation of the response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012).

10.1.2 Secondary Endpoints

Efficacy:

- PFS: defined as time from first dose of BGB-3111 until first documentation of progression (by IWWM criteria) or death, whichever comes first.
- ORR: defined as the proportion of subjects with a minor, partial, very good partial, and complete response.
- DOMR: defined as the time from the date that the major response criteria are first met to the date that PD is objectively documented or death, whichever occurs first.
- Resolution of treatment precipitating symptoms, defined as absence of symptoms at any point during study treatment.
- Anti-lymphoma effect is defined as any reduction during the course of study treatment in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly by CT scan. Lymphadenopathy is defined as any node with LDi > 1.5 cm and splenomegaly is defined as vertical spleen length > 13 cm.

Safety:

To evaluate the safety and tolerability of BGB-3111, as defined by:

- The incidence and severity of TEAEs, SAEs and treatment-related AEs according to CTCAE v4.03
- The incidence, severity, and causation of adverse events leading to study drug discontinuation, dose reduction and dose interruption.

10.1.3 Exploratory Endpoints

- Overall survival defined as the time from the date of first dose of BGB-3111 until date of death from any cause.
- CR plus VGPR rates in subjects with $MYD88^{MUT}$ WM.
- Identification of potential resistance biomarkers and mechanisms: paired bone marrow aspiration (prior to treatment initiation and at relapse) will be used to identify potential biomarkers and mechanisms.

10.2 Statistical Analysis

10.2.1 Analysis Populations

Subjects who are clinically benefitting from treatment with BGB-3111 despite meeting the criteria for PD based on IgM findings can continue to receive treatment with BGB-3111and be followed for safety.

The Safety Population (SP) includes all subjects who received at least one dose of BGB-3111; this population will be used for all safety analyses.

The Revised Safety Population (RSP) includes subjects with pathologically confirmed WM among those in the SP; this population will be used for all efficacy analyses.

The Per-Protocol Population (PP) includes subjects who received any dose of BGB-3111 and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. The PP population will be used for select efficacy analyses.

10.2.2 Subject Disposition

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

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

10.2.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial WM diagnosis; categorical variables include sex, age group (< 65 vs. ≥ 65), disease stage, ECOG-performance status, prior line of therapy for WM, MYD88/CXCR4 mutation status, baseline bone marrow involvement (< 50% vs. ≥ 50%), WM International Prognostic Scoring System (IPSS) (low, intermediate, high), β_2 microglobulin (≤ 3 mg/L vs. > 3 mg/L).

10.2.4 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the WHO-DD drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

10.2.5 Efficacy Analyses

10.2.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is MRR, defined as the proportion of subjects who achieves CR + VGPR + PR, to be assessed by an IRC according to an adaptation of the response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012) (Appendix 3).

In this population, MRR in the historical control is assumed to be approximately 30% based on recent trials. The MRR in this study is estimated as 60%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: major RR=30%
Ha: major RR ≥ 30%

A binomial exact test will be performed for hypothesis testing in the safety population. If the obtained 1-sided p-value is less than or equal to 0.025, it will be concluded that the single agent BGB-3111 statistically significantly increases major RR compared with historical control. Therefore, the superiority of single agent BGB-3111 will be demonstrated.

A two-sided Clopper-Pearson 95% confidence interval (CI) of major RR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed. Subsequent analyses will be performed when mature secondary efficacy endpoints are available.

10.2.5.2 Secondary Efficacy Analysis

Overall response rate (ORR as determined by IRC review. Overall response rate, defined as the proportion of subjects who achieves CR, VGPR, PR, and minor response (MR) according to an adaptation of the response criteria updated at the 6th IWWM (Owen et al 2013; NCCN Guidance Insights, 2012) by an IRC, will be estimated in the Safety Population. Clopper-Pearson 95% CI will be constructed for calculating exact binomial interval for ORR.

Best overall response (BOR) is defined as the best response recorded from the start of BGB-3111 until data cut or start of new anti-cancer treatment. Subjects with no post-baseline response assessment (due to whatever reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, VGPF, PR, MR, SD, and PD) will be presented.

PFS is 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.

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

Median PFS, if estimable, will be estimated using the Kaplan-Meier method. Its 2-sided 95% CIs, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Kaplan-Meier estimates of PFS will be plotted over time. The PFS at 6 months, defined as the percentage of subjects in the analysis population who remain alive and progression-free at the specified time point, will be estimated using Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926).

DOMR is defined as the time from the date that the major response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. It will be analyzed similarly as PFS.

Resolution of cytopenias, organomegaly, neuropathy, and maximum decrease in percentage of lymphoplasmacytoid lymphocytes in bone marrow will be summarized descriptively at each visit.

10.2.5.3 Exploratory Efficacy Analysis

OS is defined as the time from the starting date of BGB-3111 to the date of death due to any reason. Subjects who are known to be alive as of their last known status will be censored at their date of last contact. OS will be similarly analyzed using the Kaplan-Meier method.

CR plus VGPR rates will be determined in patients with $MYD88^{MUT}$ as the proportion of patients who achieve VGPR or CR.

10.2.5.4 Subgroup Analysis

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: sex, age group (< 65 vs. ≥ 65), ECOG-performance status (0 vs. ≥ 1), prior line of therapy for WM (0 vs. ≥ 1), MYD88/CXCR4 mutation status, baseline bone marrow involvement (< 50% vs. ≥ 50%), WM International Prognostic Scoring System (IPSS) (low, intermediate, high), β2 microglobulin (≤ 3 mg/L vs. > 3 mg/L). Within group values (rates or means/medians) will be presented in forest plots.

10.2.6 Biomarker/Pharmacodynamic Data, If Applicable

The mutational status of the MYD88 and CXCR4 genes has been shown to predict responsiveness of the BTK inhibitor ibrutinib in WM (Treon et al 2015). All subjects will have mutation analysis of MYD88 and CXCR4 performed on bone marrow samples which will be sent to the central laboratory.

10.3 Safety Analyses

Safety will be assessed by monitoring and recording of all AEs including all CTCAE v4.03 grades (both increasing and decreasing severity), regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs and performance of PEs. Descriptive statistics will be used to analyze all safety data in the Safety Population.

10.3.1 Extent of Exposure

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

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

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

10.3.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim

term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and preferred term (PT), even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship. Serious adverse events, deaths, TEAE with Grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Incidence and time to diarrhea (≥ Grade 3), severe bleeding (defined as ≥ Grade 3 bleeding of any site or CNS bleeding of any grade), atrial fibrillation, and TEAEs leading to study drug discontinuation will be summarized.

10.3.3 Laboratory Analyses

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

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

10.3.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate,

respiratory rate, temperature, weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subject and visit.

10.3.5 Electrocardiogram

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

10.4 Sample Size Consideration

The sample size calculation of 40 subjects was based on the precision of a MRR estimate and the power of the comparison to the historical rate, under assumed MRR of 60% in the study as compared to 30% in the historical control (95% CI is 43.3%, 75.1%). Using a binomial exact text, the power is >0.969 with 40 subjects to demonstrate statistical significance at a 1-sided alpha of 0.025 under above assumption.

If the observed MRR is 60%, its 95% exact CI from 40 patients will be (43.3%, 75.1%).

10.5 Interim Analysis

An interim analysis is not planned.

10.6 Other Statistical Issues

Primary, secondary and exploratory endpoints will be summarized in the Safety Population. In the analyses described above and any other sensitivity analysis, subjects with missing data will be considered as non-responders and will be included in the denominator when calculating MRR/ORR. Non-responders will be excluded in the analysis of DOMR.

A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the statistical analysis plan (SAP).

Any other statistical/ analytical issues will be discussed in the SAP.

11. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory Authority Approval

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

11.2 Investigator Responsibilities

11.2.1 Good Clinical Practice

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

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

11.2.2 Ethical Conduct of the Study and Ethics Approval

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

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

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

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

11.2.3 Informed Consent

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

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

11.2.4 Investigator Reporting Requirements

As indicated in Section 9.3.3, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5 Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

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

11.2.6 Case Report Forms

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

11.2.7 Drug Accountability

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

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

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

11.2.8 Inspections

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

11.2.9 Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

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

11.3.2 Study Report and Publications

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

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

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

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

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

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

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

11.4 Study and Study Center Closure

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

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

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

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

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

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

11.5 Records Retention and Study Files

11.5.1 Study Files and Retention of Records

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

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

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

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

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

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

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

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

11.6 Provision of Study Results and Information to Investigators

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

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

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

11.7 Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

11.8 Joint Investigator/Sponsor Responsibilities

11.8.1 Access to Information for Monitoring

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

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

11.8.2 Access to Information for Auditing or Inspections

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

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13. APPENDICES

Appendix 1 Signature of Investigator

PROTOCOL TITLE: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects with Relapsed/Refractory Waldenström's Macroglobulinemia (WM)

PROTOCOL NO: BGB-3111-210

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Appendix 2 Medications Which are Known to Prolong The QT Interval and/or Induce Torsades De Pointes to Be Avoided

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

Appendix 3 Categorical Response Definitions (modified Owen 2013)

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baselines No histological evidence of bone marrow involvement
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline [a] Improvement in extramedullary disease, ie, lymphadenopathy/splenomegaly 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 [a] Improvement in extramedullary disease, ie, 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 [a] No new signs or symptoms of active disease
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	At least one of the following: • Confirmed ≥ 25% increase in serum IgM and total increase of ≥ 500 mg/dL from nadir (on treatment) [a,b] • New lymph nodes >1.5 cm, or ≥ 50% increase from nadir in SPD of >1 node, or ≥ 50% increase in longest diameter of a previously identified node >1 cm in short axis • New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

[a] Sequential changes (separated by at least 4 weeks) in IgM levels should be determined by the IgM value from the quantitative serum immunoglobulin assay, unless for assay limitations this is not possible, in which case the M protein level by densitometry (SPEP) will be used

[b] Isolated increase in serum IgM levels during periods of study drug withholding will not be considered as progressive disease unless confirmed by a repeat serum IgM level at least 10 weeks after restarting study drug administration and accompanied by a total increase of at least 500mg/Dl from lowest nadir. Please see guidelines for specific clinical or laboratory circumstances below.

c For response assessments that occur during cycles where a CT scan is not required then results from prior scans (up to 12 weeks during the first 48 weeks and up to 24 weeks thereafter) can be carried forward in those subjects with extramedullary disease at baseline.

Guidelines for specific clinical or laboratory circumstances:

1. *Baseline serum total IgM value above the central laboratory limit of quantitation.*

   If the baseline central laboratory serum total IgM value exceeds the upper limit of quantitation, the M-protein value, by central assessment, will be used for response determination throughout the study.

2. *Baseline serum total IgM value, by central assessment, is not interpretable due to technical reasons.*
   If the baseline central laboratory serum total IgM value is not interpretable due to technical reasons, the central laboratory serum M-protein value will be used of response determination throughout the study. In cases where both the central laboratory total serum IgM and M-protein values are not interpretable due to technical reasons, the local serum total IgM (or local M-protein value, in cases where the local serum total IgM value exceeds the upper level of quantitation) will be used for response assessment throughout the study.

3. *Subjects with documented cryoglobulinemia.*

   For subjects with abnormal cryoglobulin result at baseline confirmed by the central lab, the local lab will test for the presence of cyroglobulins along with testing the serum quantitative immunoglobulins under warm conditions throughout the study. This is to ensure that the same methodology is used throughout the study. Only when serum immunoglobulin cannot be quantified, serum immunoelectrophoresis sample will need to be re-collected and processed at local laboratory under warm conditions.

4. *Plasmapheresis*

   Subjects may undergo plasmapheresis, when clinically indicated, during the first two cycles of study treatment. A pre-plasmapheresis serum total IgM and M-protein must be obtained during the screening period, and will serve as the baseline value for response assessment throughout the study. Response determination will commence 4 weeks following the last plasmapheresis procedure and will be based upon the baseline pre-plasmapheresis serum total IgM or M-protein value (according to the guidelines above). Subjects requiring plasmapheresis after cycle 2 will be adjudged to have progressive disease.

5. *Assigning Response in the Case of Drug Hold*

   For the definition of IgM flare: A response assessment of “IgM flare” will be assessed instead of “PD” after Study drug has been held at least 3 consecutive DAYS and there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an “apparent” response of progressive disease (PD). The period that this is applicable begins on the day of the first missed dose and ends when the subject has IgM levels or extramedullary disease that no longer qualify as “apparent” PD (e.g An increase in serum IgM level of at

least 25 percent and 500mg/dL from lowest nadir) or the subject has a confirmed response of PD*, whichever comes first.

During and following periods of study drug with-holding, response assessments that would otherwise qualify as PD* will initially be recorded as IgM Flare and NOT be considered as progressive disease. When assigning response for IgM Flare, the following conditions must be met:

a) IgM levels/known extramedullary are decreasing from peak after a drug hold.

b) If after 10 weeks of study drug reinitiation the next assessed IgM level shows either no decrease or continued rise, then a serum IgM level must be obtained 4 weeks later to confirm PD. If PD is confirmed then a response assessment of PD* will be recorded.

c) Similarly, if apparent PD was due to an increase in extramedullary disease and after 10 weeks of study drug reinitiation the evaluation of extramedullary shows either no decrease or continued rise, then a PD is confirmed and a response assessment of PD will be recorded.

d) If after 10 weeks of study drug reinitiation the IgM level decreases and then rises at any timepoint within the drug holding period:
   - If at the time of the IgM rise, the IgM level still qualifies as PD* then a confirmatory serum IgM level must be obtained 4 weeks later to confirm PD*. The response of PD will be recorded at the time of the initial IgM rise.
   - If at the time of the IgM rise, the IgM level does not qualify as PD* then continue response assessments as per protocol.

Of note, in the setting of multiple drug holds the nadir continues to be the lowest achieved serum IgM level on study for purposes of response assessment.

*PD is defined per protocol as an increase in serum IgM level of at least 25 percent and 500mg/dL from lowest nadir

6. *Missing CT Scans*

If a required CT scan timepoint is missed, it should be performed as soon as possible. In cases where a single CT scan timepoint is missed and the subsequent CT scan findings remain the same or improved from the prior scan, response can be assessed for the intervening cycles using the CT scan obtained prior to the missed CT scan. If 2 consecutive CT scan timepoints are missed, then the best response that can be assessed during those cycles is an MR (minor response).

Appendix 4 Prohibited Medications (CYP3A Inhibitors and CYP3A Inducers)

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)

Appendix 5 Sensitive CYP2C8, CYP2C9, and CYP2C19 Substrates or CYP2C8, CYP2C9, and CYP2C19 Substrates With a Narrow Therapeutic Index

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

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

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

Appendix 6 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 7 Central Laboratory Tests (can include but not limit to the following tests)

1. **Serum M protein examinations:**
   a. Immunoglobulins: IgG, IgA, IgM
   b. Serum immunoelectropheresis
   c. Serum immunofixation
   d. Serum β2-microtubulin
2. **Urinary M protein examinations:**
   a. Urinary immunoglobulins: κ, λ
   b. Urinary immunofixation
   c. Urinary β2-microtubulin
3. **Bone marrow aspiration flow cytometry:**
   Suggest using B cell and plasma cell surface marker tests, can include the following markers:
   CD3, CD5, CD8, CD10, CD19, CD20, CD23, CD45, CD56
   CD43, CD79b, CD38, CD138, CD200, CD117, FMC7, CD103, sκ, s λ , cκ, c λ , sIgM, sIgD.
4. **Bone marrow biopsy IHC**
   Can include the following markers: CD3, CD20, CD138, κ, λ, pax5, CD5, CD10, CD23, cyclinD1, CD38, CD56.
5. **MYD88, CXCR4 Mutation analysis**

Appendix 8 New York Heart Association Classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.