NCT03053440

CLINICAL STUDY PROTOCOL

Protocol Title:	**A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)**
Protocol Number:	**BGB-3111-302**
Study Phase:	**3**
Investigational Product:	**Zanubrutinib (BGB-3111)**
Original Protocol:	**29 July 2016**
Amendment 1:	**01 November 2016**
Amendment 2:	**08 May 2017**
Amendment 3:	**02 February 2018**
Amendment 4:	**21 September 2018**
Amendment 5:	**26 August 2019**
IND No.:	**125326**
EudraCT No.:	**2016-002980-33**
Sponsor:	**BeiGene, Ltd.** **c/o BeiGene USA, Inc.** **2955 Campus Drive, Suite 200** **San Mateo, CA 94403** **USA**
Medical Monitor:	[redacted]

[redacted]

SIGNATURES

PROTOCOL TITLE: A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)

PROTOCOL NO: BGB-3111-302

BeiGene Approval:

[redacted]

September 2, 2019

Date

Sponsor Medical Monitor

SYNOPSIS

Name of Sponsor/Company:	**BeiGene USA, Inc.**
Name of Finished Product:	**Zanubrutinib (BGB-3111)**
Name of Active Ingredient:	**Zanubrutinib (BGB-3111)**
Title of Study:	A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)
Protocol No:	BGB-3111-302
Study Centers:	Approximately 82 sites in the United States (US), Australia (AUS), the European Union (EU), and others
Study Phase:	Phase 3
Treatment Duration:	Subjects will receive daily treatment during the study until progressive disease (PD), unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by Sponsor.

Objectives:

Primary (Cohort 1)

- To compare the efficacy of zanubrutinib (also known as BGB-3111) vs ibrutinib in subjects with activating mutations in the myeloid differentiation primary response gene 88 (MYD88) (*MYD88*^{MUT}) WM

Secondary (Cohort 1)

- To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib vs ibrutinib in subjects with *MYD88*^{MUT} WM
- To evaluate safety and tolerability of zanubrutinib versus ibrutinib in subjects with *MYD88*^{MUT} WM, as measured by the incidence and severity of adverse events according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Exploratory

[redacted]

Study Design:

This is a Phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors zanubrutinib and ibrutinib in subjects with Waldenström's Macroglobulinemia (WM) who require therapy according to the consensus panel criteria from the Seventh International Workshop on Waldenström's Macroglobulinemia (Seventh IWWM, Dimopoulos et al 2014). The study is composed of an initial Screening Phase (up to 35 days), a Treatment Phase, and a Follow-up Phase.

Approximately 210 subjects will be enrolled on the study. All subjects enrolled on the study will have baseline bone marrow samples (bone marrow aspirate and biopsy) collected and assayed at a central laboratory for sequencing of the *MYD88* gene. Approximately one hundred eighty-eight WM subjects (Approximately 150 relapsed/refractory and approximately 38 treatment-naïve subjects) with the *MYD88* mutation ($MYD88^{MUT}$), which is characteristic of WM and present in approximately 90% of cases, will be enrolled onto Cohort 1 and randomized to one of two treatment arms (Cohort 1: zanubrutinib treatment [Arm A] or ibrutinib treatment [Arm B]) in a 1:1 ratio and stratified using CXC-chemokine receptor 4 *(CXCR4*) gene sequencing status ($CXCR4^{WHIM}$ vs $CXCR4^{WT}$ vs missing) and prior line of therapy for WM (0 vs 1-3 vs >3 lines of therapy).

Subjects found to have *MYD88* wild-type ($MYD88^{WT}$) by gene sequencing, which is estimated to be present in approximately 10% of enrolled subjects, will be enrolled to Cohort 2 and will receive zanubrutinib treatment on a third, non-randomized, study arm (Arm C). In addition, those subjects whose MYD88 mutational status is missing or inconclusive will be assigned to Cohort 2, Arm C. Approximately 22 total subjects (including relapsed/refractory and treatment-naïve subjects) are anticipated to be enrolled in this cohort.

The primary efficacy analysis will be conducted approximately 12 months after the last relapsed/refractory subject is randomized.

- Response will be assessed by an independent review committee (IRC) according to an adaptation of the response criteria updated at the Sixth International Workshop on Waldenström's Macroglobulinemia (Sixth IWWM, Owen et al 2013 and National Comprehensive Cancer Network [NCCN] Guidelines, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia 2015: v2). Response assessments will occur at the beginning of every cycle (i.e., every 4 weeks starting from C2D1) for the first 48 weeks and then every 3 cycles thereafter until PD.

- Serum IgM and M-protein levels will be measured at Screening, on Day 1 of every cycle for the first 48 weeks, then every 3 cycles thereafter (each cycle is 28 days).

- For subjects with evidence of extramedullary disease (defined as lymphadenopathy [lymph nodes having a long axis of > 1.5 cm] and/or splenomegaly) detected by computed tomography (CT) scan at baseline:

    - Response assessment by CT scan will occur every 12 weeks during the first 48 weeks beginning on Day 1, Cycle 4, and then every 24 weeks until PD or complete resolution of extramedullary disease. Additionally, a CT scan is also required at the safety follow-up visit.
      For response assessments that occur during cycles when a CT scan is not required, the results of the most recent CT scan may be used for the response assessment only if the

prior scan date is within 12 weeks of the response assessment date during the first 48 weeks of the study and within 24 weeks of the response assessment date thereafter.

- QOL will be measured every 12 weeks during the first 48 weeks, and then every 24 weeks thereafter by the EORTC QLQ-C30 and EQ-5D in *MYD88*^{MUT} WM subjects.
- Bone marrow involvement by WM will be assessed by aspirate and biopsy at Screening, at the end of Cycle 12 (Week 48), at time of suspected complete response (CR), and as clinically indicated.
- All subjects will be followed for adverse events (AEs) until 30 days after the last dose of study drug. All treatment-related AEs and serious AEs (SAEs) will be followed until resolution or stabilization. Efficacy evaluations will continue until documented PD for subjects who discontinued for reasons other than PD.

Planned Number of Subjects:	Approximately 210 subjects will be enrolled. This includes approximately 188 subjects (approximately 150 subjects with relapsed/refractory WM and approximately 38 subjects with treatment-naïve WM) with *MYD88*^{MUT} enrolled in Cohort 1 and randomized 1:1 to either Arm A or Arm B, and approximately 22 total subjects (both relapsed/refractory and treatment-naïve) who are *MYD88* wild-type (*MYT88*^{WT}) enrolled in Cohort 2, Arm C.

Study Population

Inclusion criteria

1. Clinical and definitive histologic diagnosis of WM. Subjects must either have relapsed/refractory disease OR be treatment naïve and considered by their treating physician to be unsuitable for standard chemoimmunotherapy regimens
    - For subjects who have received no prior therapy for WM: "Unsuitable" for treatment with a standard chemoimmunotherapy regimen must be a physician-determined status based on co-morbidities and risk factors. Physicians will need to provide and document organ system(s) and specific reason(s) for subject being considered unsuitable. Patient preference does not meet the eligibility requirement for a treatment-naïve subject to be unsuitable for treatment with a standard chemoimmunotherapy regimen
2. Meeting at least one criterion for treatment according to consensus panel criteria from the Seventh IWWM (Dimopoulos et al 2014, Table 4)
3. Measurable disease, as defined by a serum IgM level > 0.5 g/dl
4. Age ≥ 18 years old
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
6. Adequate bone marrow function defined as:
    - Neutrophils ≥ 0.75 x 10^9/L, independent of growth factor support within 7 days of study entry
    - Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of study entry

7. Creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]) based on ideal body mass
8. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN)
9. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome)
10. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Subjects with factor inhibitors that prolong PT/aPTT without increasing the bleeding risk, or those with lupus anticoagulant or acquired von Willebrand's syndrome due to WM may be enrolled after discussion with the Medical Monitor or designee.
11. Subjects who relapse after autologous stem cell transplant are eligible if they are at least 3 months after transplant and are eligible after allogeneic transplant if they are at least 6 months post-transplant. To be eligible after either type of transplant, subjects should have no active infections or, in the case of allogeneic transplant relapse, no active acute graft versus host disease (GvHD) of any grade, and no chronic GvHD other than mild skin, oral, or ocular GvHD not requiring systemic immunosuppression
12. Female subjects of childbearing potential and non-sterile males must practice highly effective methods of birth control initiated prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug. These methods include the following:
    - A barrier method of contraception (including male and female condoms with or without spermicide) plus one of the following hormonal contraceptives:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
            - Oral, intravaginal or transdermal
        - Progestogen-only hormonal contraception associated with the inhibition of ovulation
            - Oral, injectable, implantable
        - An intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug). Total sexual abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product (IMP), and withdrawal are not acceptable methods of contraception.
13. Of note, barrier contraception (including male and female condoms with or without spermicide)

is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above. Life expectancy of > 4 months

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

Exclusion criteria

1. Prior exposure to a BTK inhibitor
2. Evidence of disease transformation at the time of study entry
3. Corticosteroids given with antineoplastic intent within 7 days, or chemotherapy given with antineoplastic intent, targeted therapy, or radiation therapy within 4 weeks, or antibody-based therapy within 4 weeks of the start of study drug
4. Major surgery within 4 weeks of study treatment
5. Ongoing toxicity of ≥ Grade 2 from prior anticancer therapy (except for alopecia, absolute neutrophil count [ANC] and platelets). For ANC and platelets, please follow inclusion criteria #6 regarding neutrophils and platelets
6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent
7. Currently active, clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease (congestive heart failure) as defined by the New York Heart Association (NYHA) Functional Classification, or history of myocardial infarction within 6 months of screening
8. QTcF prolongation (defined as a QTcF > 480 msec)
9. Active, clinically 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 (GI) function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
11. Uncontrolled active systemic infection or recent infection requiring parenteral anti-microbial therapy that was completed ≤ 14 days before the first dose of study drug
12. Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or hepatitis C infection as follows:
    a) Presence of hepatitis B surface antigen (HBsAg) or anti-hepatitis B core antibody (anti-HBc). Patients with anti-HBc, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable and if they are willing to undergo monthly monitoring for HBV reactivation
    b) Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV ribonucleic acid (RNA) is undetectable

13. Pregnant or lactating women
14. Any life-threatening illness, medical condition, organ system dysfunction, need for profound anticoagulation, or bleeding disorder, which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk
15. Inability to comply with study procedures
16. At time of study entry, taking any medications which are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers.
17. At time of study entry, taking warfarin or other vitamin K antagonists
18. Known central nervous system (CNS) hemorrhage or stroke within 6 months prior to study entry
19. Active CNS involvement by WM. Patients with a previous history of CNS involvement must undergo magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology studies to document no evidence of CNS disease prior to study entry.
20. History of intolerance to the active ingredients or other ingredients of either zanubrutinib or ibrutinib

Study Drug:	Zanubrutinib 160 mg (80 mg x 2 capsules) twice daily (BID), administered orally (PO)
Comparator:	Ibrutinib 420 mg (140 mg x 3 capsules or in other applicable dose forms) once daily (QD), administered PO

Study Treatment:

Subjects will be divided into two cohorts according to *MYD88* sequencing at Screening.

Subjects in Cohort 1 (subjects with *MYD88* ^{MUT} by gene sequencing) will be randomized 1:1 to receive:

Arm A

Zanubrutinib 160 mg (80 mg x 2 capsules) administered PO BID at approximately the same time each day with at least 8 hours' interval. A treatment cycle consists of 28 days.

Arm B

Ibrutinib 420 mg (140 mg x 3 capsules or in other applicable dose forms) administered PO QD at approximately the same time each day. A treatment cycle consists of 28 days.

[redacted]

Dose Modifications:

The guidelines set forth in the table below should be followed for dose interruption or modification of zanubrutinib or ibrutinib for hematologic or non-hematologic toxicities noted on investigator assessment of study drug relatedness.

Study drug (zanubrutinib or ibrutinib) may be held for a maximum of 2 consecutive cycles and restarted upon resolution of toxicity and per investigator discretion. If, in the investigator's opinion, it is in the subject's best interest to restart study drug after dose has been held for more than 2 consecutive cycles, then written approval must be obtained from the Sponsor Medical Monitor or designee. More than one

study drug hold is allowed.

Zanubrutinib and Ibrutinib Dose Reduction Steps

Toxicity Occurrence	Dose Level	Zanubrutinib Dose (Arms A and C) (Starting dose = 160 mg BID)	Ibrutinib Dose (Arm B) (Starting dose = 420 mg QD)
First	Starting Dose	Restart at 160 mg BID	Restart at 420 mg QD
Second	Dose Level -1	Restart at 80 mg BID	Restart at 280 mg QD
Third	Dose Level -2	Restart at 80 mg QD	Restart at 140 mg QD
Fourth	Discontinue study drug	Discontinue zanubrutinib	Discontinue ibrutinib

BID=twice daily; QD=once daily

Dose Modifications for Hematologic Toxicity for Zanubrutinib

For zanubrutinib, dosing will be held for hematologic toxicity suspected to be related to study drug treatment under any of the following conditions:

- Grade 4 neutropenia (lasting >10 days despite the use of growth factors)
- Grade 4 thrombocytopenia (lasting > 10 days)
- ≥ Grade 3 febrile neutropenia
- ≥ Grade 3 thrombocytopenia associated with significant bleeding

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

Dose Modifications for Non-Hematologic Toxicity for Zanubrutinib

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

Zanubrutinib should be held for any ≥ Grade 3 bleeding. The drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in gastrointestinal [GI] bleed) and the risk of a re-bleed is deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should **not be** resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anti-coagulation or anti-platelet medications (except low dose aspirin or low molecular weight heparin

used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor.

Dose Modifications for Ibrutinib

For dose modification of ibrutinib, local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) should be followed throughout the study. The major dose modifications for ibrutinib are described below:

Ibrutinib should be interrupted for any new onset or worsening of ≥ Grade 3 non-hematologic toxicities, ≥ Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib therapy may be re-initiated at the starting dose. If the toxicity recurs, drug dose will be reduced to Dose Level -1 (280 mg orally QD). A second dose reduction to Dose Level -2 (140 mg orally QD) may be considered as needed. If these toxicities persist or recur following 2 dose reductions, the subject will be discontinued for study treatment.

As with zanubrutinib, ibrutinib should be interrupted for any Grade ≥ 3 bleeding. The drug should be permanently discontinued for any related Grade ≥ 3 hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in GI bleed) and the risk of a re-bleed is deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should not be resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anti-coagulation or anti-platelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor.

Use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used.

Concomitant use of ibrutinib with strong and moderate CYP3A4 inhibitors should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, ibrutinib dose must be reduced or withheld temporarily (7 days or less). Ibrutinib dose must be reduced when administered with moderate CYP3A inhibitors. Refer to the local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) for specific instructions on dose modifications with these inhibitors.

For patients with mild hepatic impairment (Child-Pugh Class A) and patients with moderate hepatic impairment (Child-Pugh Class B), refer to the local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) for specific instructions on dose modifications for ibrutinib. It is not recommended to administer ibrutinib to patients with severe hepatic impairment (Child-Pugh Class C).

Concomitant Therapy and Clinical Practice:

Permitted Concomitant Therapy

Corticosteroid courses of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition.

Bisphosphonates can be coadministered with zanubrutinib.

Infection prophylaxis should be as per institutional standards.

Prohibited Concomitant Therapy

Any anticancer chemotherapy, immunotherapy, corticosteroids given with antineoplastic intent,

experimental therapy, and radiotherapy are prohibited. Corticosteroid courses of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition. The chronic use of corticosteroids at doses equivalent to adrenal replacement (2.5 mg to 7.5 mg prednisone) is prohibited without previous discussion and approval from the Medical Monitor or designee.
Use of warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib.
Supplements such as fish oil or supplements and vitamin E preparations should be avoided.
Use of preparations containing St. John's Wort should be avoided.

Concomitant Use of CYP Inhibiting/Inducing Drugs
The primary metabolic pathway for both zanubrutinib and ibrutinib involve the cytochrome P450, family 3, subfamily A (CYP3A) isoform. Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 3 and Table 2 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib/ ibrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification guidelines for zanubrutinib in Table 2 and refer to the ibrutinib local prescribing information. The medical monitor should be consulted in these situations.

Criteria for Evaluation:

Response will be evaluated using an IRC based on an adaptation of the response criteria updated at the Sixth IWWM (Owen et al. 2013 and NCCN Guidelines, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia 2015:v2). The modified criteria are listed in Appendix 2 with guidelines for special clinical or laboratory circumstances including response assessment in the case of drug hold or missing CT scans.

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, physical examinations, and laboratory measurements (i.e., complete blood count, chemistry, and urinalysis).

Subjects will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI-CTCAE v4.03]) 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 antitumor therapy.

An independent data monitoring committee (DMC) will monitor safety and efficacy data periodically throughout the study. One interim analysis is planned, and will occur approximately 6 months after the first 50 relapsed/refractory subjects in Cohort 1 are randomized to Arms A or B. This analysis is for futility only. A stop in recruitment is not planned for this interim analysis. At regular safety reviews, data review will include but not be limited to deaths, SAEs, adverse events leading to dose reduction, dose interruption, or drug discontinuation. The DMC may recommend study modification, including termination of the study due to efficacy and safety concerns. Details of safety data review will be outlined in DMC charter.

Primary Endpoint:

Cohort 1 Only

- Proportion of subjects achieving either CR or very good partial response (VGPR), as determined by the IRC using an adaptation of the response criteria updated at the Sixth IWWM (Owen et al. 2013 and NCCN Guidelines, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia

2015: v2).

Secondary Endpoints:

Efficacy (Cohort 1):

- Major response rate (MRR) as assessed by the IRC, defined as the proportion of subjects achieving CR, VGPR, or partial response (PR)
- Duration of response (DOR) as assessed by the IRC, defined as the time from first determination of response (CR, VGPR or PR) (per modified IWWM criteria) until first documentation of progression (per modified IWWM criteria) or death, whichever comes first
- Rate of CR or VGPR as assessed by the Investigator
- DOR as assessed by the Investigator, defined as the time from first determination of response (CR, VGPR or of PR) (per modified IWWM criteria) until first documentation of progression (per modified IWWM criteria) or death, whichever comes first
- Progression-free survival (PFS) as assessed by the IRC, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first
- PFS as assessed by the Investigator, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first
- Resolution of treatment-precipitating symptoms, defined as the absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment
- Anti-lymphoma effect, defined as any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or splenomegaly by CT scan, at any time during the course of study treatment

Safety (Cohort 1):

- The incidence, timing, and severity of treatment-emergent AEs (TEAE) according to NCI-CTCAE v4.03

Exploratory Endpoints:

[redacted]

[redacted]

Statistical Methods:

All inferential statistics described in this Section refer to the efficacy comparisons of Arms A and B in Cohort 1, which represent the primary/secondary objectives of the study. Separate descriptive statistics in Cohort 2 will be used to report the efficacy and safety of zanubrutinib in Arm C.

Analysis Sets:

The Intent to Treat analysis set (ITT) includes all enrolled subjects who are assigned to a treatment arm. The Relapsed/Refractory analysis set (a subset of the ITT analysis set) includes all randomized subjects with at least 1 prior line of therapy as determined by the Interactive Response Technology system. The Relapsed/Refractory analysis set for Cohort 1 will be the primary analysis set used for efficacy analyses.

The Safety analysis set includes all subjects who received any dose of zanubrutinib or ibrutinib. Subjects will be assigned to the treatment arms as treated. The Safety analysis set will be used for all safety analyses.

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

The PK analysis set includes all subjects who have at least one post-dose zanubrutinib concentration.

Primary Efficacy Analysis:

The primary endpoint of CR/VGPR rate will be assessed by an IRC, based upon the best overall response (BOR), defined as the best response recorded from the cohort assignment date until data cut or start of new antineoplastic treatment, and will be analyzed in the Relapsed/Refractory analysis set and ITT analysis set of Cohort 1.

Comparison of the primary endpoint between Arm A and Arm B in Cohort 1 will be tested using hierarchical fixed-sequence procedure under the null and alternative hypotheses as follows:

H_0: $RR_A = RR_B$

Ha: $RR_A > RR_B$

where RR_A is the CR/VGPR rate in relapsed/refractory subjects in Arm A (zanubrutinib) and RR_B is the CR/VGPR rate in relapsed/refractory subjects in Arm B (ibrutinib).

Testing for above hypotheses will be performed in the Relapsed/Refractory analysis set first at 1-sided alpha of 0.025. If the result is in the Relapsed/Refractory analysis set is statistically significant, the primary objective has been met and further testing will be performed in the ITT analysis set at 1-sided alpha of 0.025.

A Cochran-Mantel-Haenszel (CMH) test of rate difference adjusting for stratification factors (CXCR4

status [WHIM vs WT/missing] and prior line of therapy [1-3 vs >3 for Relapsed/Refractory analysis set analysis and 0 vs 1-2 vs >3 in ITT analysis set analysis]) will be performed for hypothesis testing at the level of 0.025 (1-sided) in corresponding analysis sets.

A CMH 95% stratified confidence interval (CI) of rate difference (RR_A-RR_B) with each rate weighted by the number of subjects in each stratification factor combination will be constructed. A Clopper-Pearson 95% CI of CR/VGPR rate within each arm will be constructed.

The primary efficacy analysis in Cohort 1 will be conducted approximately 12 months after the cohort assignment of the last relapsed/refractory subject.

Secondary Efficacy Analyses:

If the primary efficacy analysis is significant in Cohort 1, secondary endpoints will be tested in the analysis set where the null hypothesis for primary efficacy endpoint is rejected.

MRR will be tested for non-inferiority (NI) (Arm A vs Arm B). The null and alternative hypotheses of MRR are set as follows:

H_0: MRR_A-$MRR_B \leq$-8%

Ha: MRR_A- MRR_B>-8%

where MRR_A is the major response rate in Arm A (zanubrutinib) and MRR_B is the major response rate in Arm B (ibrutinib).

MRR assessed by IRC will be compared between Arms A and B. It will be analyzed using the same methods as described for the primary endpoint, based upon the best overall response, defined as the best response recorded from the date of cohort assignment until data cut or start of new antineoplastic treatment. Subjects with no post-baseline response assessment (regardless of reason) will be considered non-responders for best overall response.

A CMH test of rate difference adjusting for stratification factors (*CXCR4* status [WHIM vs WT/missing] and prior line of therapy [1-3 vs >3 for Relapsed/Refractory analysis set and 0 vs 1-2 vs >3 in ITT analysis set]) will be performed for hypothesis testing. Non-inferiority will be concluded when the one-sided p-value is less than or equal to 0.025, or equivalently, when the 2-sided 95% CI for the weighted rate difference (weighted by the number of subjects in each stratification factor combination) excludes -8%. Furthermore, superiority can be claimed if the lower limit excludes 0.

Justification of non-inferiority margin

Since no randomized trial has been conducted in WM, the ibrutinib treatment benefit over placebo can only be estimated from the single-arm ibrutinib Phase 2 trial in which the MRR is 0.73 with 95% CI (0.60, 0.83). As a $\geq$ 50% reduction of IgM is impossible without treatment, MRR can be considered 0% in the placebo treated subject. Therefore, the lower bound of 95% CI (i.e., 60%) can be used as the treatment effect of ibrutinib over placebo (M1). A NI margin of 8% (M2) is proposed assuming 86.7% of the ibrutinib benefit over a placebo is retained. With close to 90% of the ibrutinib effect preserved, the 8% NI margin in MRR is clinically justified. The loss of the ibrutinib treatment benefit is well within the clinically acceptable range. It is worth noting that the NI of MRR will only be performed after the superiority of zanubrutinib over ibrutinib in CR/VGPR rate, which is closely correlated with MRR, has been demonstrated. Hence, a numerically higher MRR in zanubrutinib is certainly expected if the NI test of MRR is to be performed. The inclusion of the NI test of MRR is mainly based on the sample size consideration in a rare disease setting where statistical significance might not be shown in a superiority test with a clinically meaningful MRR difference (e.g., 12% higher MRR in zanubrutinib over ibrutinib) in 150 randomized relapsed/refractory subjects.

The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, VGPR, PR, Minor Response, stable disease [SD], and PD) by both independent review and investigator assessment will be presented.

Progression-free survival (PFS) will be estimated using the Kaplan-Meier (KM) method. PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

A stratified log-rank test with *CXCR4* mutational status and number of prior lines of therapy as strata will be used to test the PFS differences between Arms A and B. The Cox regression will be used to estimate the hazard ratio (HR) of PFS_A vs PFS_B. A 95% CI of HR in PFS will be constructed.

Median PFS, if estimable, will be estimated using the KM method. Its 2-sided 95% CI, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. KM estimates of PFS will be plotted over time. The PFS at 12 and 18 months, defined as the percentages of subjects in the analysis set who remain alive and progression-free at the specified time points, will be estimated using KM method along with the corresponding 95% CI constructed using Greenwood's formula.

The duration of CR/VGPR/PR within subjects who have achieved a major response will be analyzed similarly as PFS.

Indications for initiation of therapy (see Table 4) will be documented for all subjects at baseline visit. Symptoms that triggered treatment will be followed at, during, and end of treatment visits until resolution. Percentages of subjects with resolution of each and all baseline symptom(s) will be summarized; and compared between Arms A and B using Fisher's Exact test.

Maximum decrease in percentage of lymphoplasmacytoid lymphocytes by bone marrow studies will be compared using analysis of variance model with treatment arm (A vs. B) as group variable. Percentage of subjects with decreased percentage of lymphoplasmacytoid lymphocytes after the start of study medication will also be compared using Fisher's Exact test. Percentages of subjects with resolution and/or reduction of pretreatment lymphadenopathy and/or splenomegaly according to CT scan will be summarized separately; and compared using Fisher's Exact test.

Exploratory Efficacy Analyses:

[redacted]

[redacted]

[redacted]

Safety Analysis:

Safety analysis will be performed by treatment arm, as well as by combining Arms A and C.

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA®) terms and graded according to the NCI-CTCAE v4.03. All treatment-emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or was worsening in severity from baseline (pretreatment) or initiation of new anticancer therapy, whichever comes first. SAEs, deaths, TEAEs with Grade 3 or above, related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

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

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

Correlation between trough plasma zanubrutinib concentration and safety endpoints may be explored.

Sample Size:

The sample size calculation is based on the comparison of the primary endpoint CR/VGPR rate in relapsed/refractory subjects in Cohort 1. Assuming RR_A=0.35 and RR_B=0.15, seventy-five subjects per arm (approximately 150 total) provide a power of 0.814 in testing RR_A versus RR_B in the Relapsed/Refractory analysis set in Cohort 1 using a normal approximation to binomial test with a two-sided significance of 0.05. Assuming MRR_A=0.90 and MRR_B=0.80, the power of demonstrating NI of zanubrutinib in the Relapsed/Refractory analysis set is 85.5% when a NI margin of 0.08 is used.

In addition to 150 replased/refractory subjects, approximately 20% (38) treatment-naïve subjects with *MYD88*^{MUT} will be enrolled in Cohort 1.

Assuming *MYD88*^{MUT} mutation is present in 90% of the enrolled subjects, approximately a total of 210 subjects will be enrolled in this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B-cell
ADCC	antigen-dependent cell-mediated cytotoxicity
AEs	adverse events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUS	Australia
AV	Atrioventricular
BCR	B-cell receptor
BID	twice a day
BOR	best overall response
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CERT	Center for Education and Research on Therapeutics
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL	apparent total body clearance of the drug from plasma
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CXCR4	CXC-chemokine receptor 4
CYP	Cytochrome

CYP3A	cytochrome P450, family 3, subfamily A
DBP	diastolic blood pressure
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOMR	duration of major response
DOR	duration of response
ECHO	echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EQ-5D	EuroQol five dimensions questionnaire
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
eGFR	estimated glomerular filtration rate
EGFR	epithelial growth factor receptor
EU	European Union
F	bioavailability (systemic availability of the administered dose)
FDA	Food and Drug Administration
FGR	Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
FRK	fyn-related kinase
GCP	Good Clinical Practice
GI	gastrointestinal
GvHD	graft versus host disease
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio

IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
ICF	informed consent form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgM	immunoglobulin M
IMP	investigational medicinal product
INR	international normalized ratio
IRAK	interleukin-1-receptor associated kinase
IRB	Institutional Review Board
IRC	independent review committee
IRT	interactive response technology
ITK	interleukin-2-inducible T cell kinase
ITT	Intent to Treat analysis set
IWWM	International Workshop for Waldenström's Macroglobulinemia
JAK3	Janus kinase 3
KM	Kaplan-Meier
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LDi	longest diameter
MCL	mantle cell lymphoma
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
MRR	Major response rate
MUT	Mutated
MUGA	Multiple Gated Acquisition scan
MYD88	myeloid differentiation primary response gene 88
MYD^{MUT}	activating mutations in the MYD88 gene
$MYD88^{WT}$	wild-type MYD88 gene
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-κB	nuclear factor-kappa B

NI	non-inferiority
NTI	narrow therapeutic index
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PLCβ2	phospholipase C-beta-2
PO	per os (orally)
PP	Per-Protocol analysis set
PR	partial response
PT	preferred term or prothrombin time
QD	once daily
QLQ	Quality of Life Questionnaire-Core 30
QOL	quality of life
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
RNA	ribonucleic acid
SAEs	serious adverse events
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SDF-1a	stromal-derived factor 1a
SDi	shortest diameter
SOC	system organ class
SOPs	standard operating procedures
SPEP	Serum immunoelectrophoresis, with M-protein quantitation by densitometry
TEAEs	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TIBC	total iron binding capacity
TLS	tumor lysis syndrome

TMD-8	transmembrane domain 8
TSTM	too small to measure
TTNT	time-to-next-treatment
TTR	time to response
ULN	upper limit of normal
US	United States
VGPR	very good partial response
WBC	white blood cell
WHIM	Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis syndrome
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia
WT	wild type
X	to be performed
zanubrutinib	BGB-3111

1 INTRODUCTION

1.1 Current Status of Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare B-cell malignancy, characterized by bone marrow infiltration with monoclonal immunoglobulin M secreting lymphoplasmacytic cells. The incidence is 5-8 cases per million, with about 1000-1500 new patients diagnosed in the USA annually. Incidence increases with age with a median age at diagnosis of 70 years for Caucasians, and slightly lower in other ethnic groups. There is a male to female preponderance, and an incidence higher in Caucasians than Africans or Asians (Gertz et al 2000; Gertz et al 2015). Activating mutations in the *MYD88* gene ($MYD88^{MUT}$), which trigger downstream interleukin-1-receptor associated kinase (IRAK)-mediated nuclear factor -kappa B (NF-κB) signaling (Treon et al 2012), are seen in approximately 90% of cases. A second set of mutations with prognostic significance is found at CXC-chemokine receptor 4 (CXCR4), the receptor for stromal-derived factor 1a (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 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 2015a).

According to the International Prognostic scoring system for WM (ISSWM), patients are stratified into low, intermediate, and high risk groups with respective 5-year survival rates of 87%, 68%, and 36%, based upon age, IgM level, β2-microglobulin level, hemoglobin, and platelet count. (Morel et al 2009).

About 75% of initially 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 hemoglobin (Hgb), extensive bone marrow infiltration, serum M-spike, and β2-microglobulin levels are significant predictors of an eventual need for therapy (Gertz et al 2015). Indications for treatment as per the IWWM-7 consensus meeting are either clinical symptoms or laboratory findings. Clinical indications for treatment include any of the following: fever, night sweats, weight loss and fatigue, hyperviscosity syndrome, bulky/symptomatic lymphadenopathy, significant hepatomegaly or splenomegaly, other symptomatic organomegaly, or peripheral neuropathy. Laboratory indications for therapy include symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic cytopenias, nephropathy, amyloidosis, or significant anemia/thrombocytopenia due to marrow replacement.

Current treatment strategies include single agent rituximab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (Jacobson et al 2013). Bendamustine plus rituximab has been shown to be an active agent with similar overall response rates to R-CHOP but with enhanced progression-free survival and better tolerability (Rummel et al 2013). Experimental agents studied in WM include bortezomib, lenalidomide, everolimus, enzastaurin, and panobinostat.

Recently, the BTK inhibitor ibrutinib was approved for the treatment of patients with WM by the FDA and by the European Medicines Agency (EMA) in adults who have received prior treatment for their disease, or in previously untreated patients for whom treatment with chemoimmunotherapy is not suitable.

1.2 Ibrutinib

Bruton's tyrosine kinase (BTK) is a signaling molecule within the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

Ibrutinib is a first-generation small-molecule BTK inhibitor that forms a covalent bond to cysteine at position 481 in the BTK active site, leading to inhibition of BTK phosphorylation at Tyr^{223} and thus inhibiting enzymatic activity.

1.2.1 Pharmacokinetics and Drug Interactions

Ibrutinib is absorbed after oral administration with a median time to maximum observed plasma concentration (T_{max}) of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state area under the plasma concentration time curve (AUC) (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib maximum observed plasma concentration (C_{max}) and AUC by approximately 2- to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting. The oral clearance is approximately 2000 and 1000 L/h in fasted and fed condition. The half-life of ibrutinib is 4 to 6 hours. The 420 mg dosage was selected to treat WM.

Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of ibrutinib was administered in non-cancer subjects, ibrutinib C_{max} increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function. Thus, subjects with moderate and severe liver impairment should avoid using ibrutinib. Ibrutinib is not significantly cleared renally, the exposure of ibrutinib is not altered in patients with creatinine clearance (CrCL) >25 mL/min. Ibrutinib can cause fetal harm when administered to a pregnant woman; it must not be taken during pregnancy and pregnancy should be avoided for 1 month after cessation of therapy.

Ibrutinib is metabolized to several metabolites primarily by cytochrome P450 (CYP), CYP3A, and to a minor extent by CYP2D6. Refer to updated Imbruvica® (Ibrutinib) Prescribing Information, August 2018, as well as Section 6.6.2 for further discussion of drug-drug interactions with ibrutinib.

1.3 Zanubrutinib (BGB-3111)

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

1.3.1 Non-Clinical Data

Zanubrutinib inhibits BTK with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomolar (nM) in biochemical assays. Cellular assays confirmed that zanubrutinib inhibited BCR aggregation-triggered BTK autophosphorylation, and blocked downstream phospholipase C-beta-2 (PLCβ2) signaling in mantle cell lymphoma (MCL) cell lines. Zanubrutinib potently and selectively inhibited cellular growth of several MCL cell lines (REC-1, Mino, and JeKo-1) and activated B-cell (ABC) type of diffuse large B-cell lymphoma (DLBCL) cell line 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 zanubrutinib induced dose-dependent antitumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib was more selective than ibrutinib for inhibition of kinase activity of BTK vs. EGFR, Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), fyn-related kinase (FRK), human epidermal growth factor receptor (HER)2, HER4, ITK, JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antigen-dependent cell-mediated cytotoxicity (ADCC). Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced ADCC, consistent with zanubrutinib being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays, thus preventing the potential for antagonism with rituximab that has been seen preclinically with other BTK inhibitors. Refer to the Investigator's Brochure (IB) for more detailed information on zanubrutinib.

1.3.2 Pharmacokinetics and Drug Interactions

In the Phase 1 study, PK was linear between 40 mg and 320 mg daily. The absorption of zanubrutinib is rapid with median time to maximum plasma concentration (C_{max}) of 2 hours. Preliminary results from the food effect study revealed that zanubrutinib exposure was not altered by high-fat breakfast, and was increased by 30-60% with standard breakfast when compared to fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg QD administered in the ongoing Phase 1 study, which did not lead to

additional safety findings. The terminal elimination half-life is approximately 4 hours at 320 mg daily.

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 daily. At the 160 mg BID dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across 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 daily dose; both schedules show a high level of activity without compromise of the tolerability profile as compared to lower doses of zanubrutinib.

Cytochrome P450, family 3, subfamily A (CYP3A) was the major CYP isoform responsible for zanubrutinib metabolism. Based on *in vitro* data, zanubrutinib is a moderate inhibitor for CYP2C8 (IC_{50} = 4.03 μM). Zanubrutinib is not a time-dependent CYP inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Zanubrutinib is not an inducer of human CYP1A2 or CYP2B6 but has weak CYP3A induction potential at a concentration equal to or higher than 3 μM in primary human hepatocytes.

1.3.3 Safety Pharmacology

The potential risk of zanubrutinib on QT interval prolongation was assessed using a battery of preclinical studies. A GLP compliant hERG assay was conducted. Based on the clinical steady-state, unbound Cmax of 0.042 μM (total Cmax 346 ng/mL; plasma protein binding 94.2%) observed at the recommended Phase 2 dose (RP2D) of 160 mg BID, there is more than a 200-fold exposure margin compared with the hERG IC50 of 9.11 μM.

No effects on blood pressure, heart rate, or electrocardiogram (ECG) findings, including QT and QTc intervals, were noted in telemetry-instrumented conscious dogs following single doses of zanubrutinib up to 100 mg/kg. In addition, no abnormal changes in ECG or cardiovascular function were noted in 28- and 91-day repeat-dose toxicity studies in dogs at doses up to 100 mg/kg. In these studies, the systemic exposure of zanubrutinib was 10-fold higher than that observed at the human therapeutic dose.

1.3.4 Clinical Pharmacology

The QT interval prolongation potential of zanubrutinib was evaluated in healthy subjects in a thorough QT study (BGB-3111-106). Results from this study demonstrated that single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including QTc intervals and other ECG intervals.

Because of the short half-life and no accumulation seen upon multiple-dosing, these results are also applicable for steady-state conditions.

Results from a dedicated clnical drug-drug interaction study (BGB-3111-104) indicate that coadministration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg every day for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$, and 12.6-fold for maximum observed plasma concentration (C_{max}), in healthy subjects. Coadministration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg every day for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. Additionally, preliminary simulations from a physiologically-based pharmacokinetic (PBPK) model suggest that coadministration of multiple doses of a moderate CYP3A inhibitor (eg, diltiazem, erythromycin, and fluconazole) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. For coadministration with a moderate CYP3A inducer (eg, efavirenz), PBPK simulations suggest that the C_{max} and AUC of zanubrutinib may decrease by approximately 2- to 3-fold.

A clinical drug-drug interaction study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), and BCRP (rosuvastatin) using a cocktail approach. The results show that zanubrutinib does not significantly affect drugs metabolized by CYP2C9 (warfarin) or transported by BCRP (statins). Zanubrutinib has a mild induction effect on CYP3A and CYP2C19 enzymes, but not an inhibitor of CYP2C19. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib. Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}.

Based a validated PBPK model to simulate the effect of zanubrutinib on the pharmacokinetics of CYP2B6 sensitive substrate, the potential for zanubrutinib to induce CYP2B6 is considered low.

Based on results of two clinical DDI studies above, a validated PBPK model was developed and was employed to simulate the effect of zanubrutinib on the pharmacokinetics of sensitive CYP2C8, and CYP2B6 substrates. The simulation findings show that concomitant use of zanubrutinib has a minimal or no effect on the exposure of CYP2C8 substrate (eg, rosiglitazone) or CYP2B6 substrate (eg, bupropion). The predicted AUC ratios of repaglinide and bupropion (with versus without zanubrutinib coadministration) are predicted to be close to 1.

Refer to the Investigator's Brochure (IB) for more detailed information of zanubrutinib.

1.4 BTK Inhibitors in the Treatment of Waldenström's Macroglobulinemia Study Rationale and Risk/Benefit Assessment

Bruton's tyrosine kinase, a member of the TEC family kinases, is a critical component of BCR signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies.

Ibrutinib, given at a dose of 420 mg PO daily, was evaluated in a 63-patient single-arm Phase 2 study. The responses were assessed by reduction in serum IgM levels from baseline according to a modification of the Sixth IWWM response criteria. (IWWM, Owen et al 2013 and NCCN Guidance Insights, 2012). The MRR (defined as achieving partial response or better at any time over the course of study treatment) was 61.9%. No patients achieved a CR. A very good partial response (VGPR; a > 90% reduction in IgM) occurred in 11.1% of patients and a partial response (PR; 50-89% reduction in IgM) in 50.8%. The median time to response was 1.2 months (range 0.7-13.4 months). In this trial, the median reduction in IgM level was from 3520 mg/dl to 880 mg/dl, and median improvement in hemoglobin was from 10.5 g/dl to 13.8 g/dl. However, there are limitations to ibrutinib in the treatment of WM. By IgM criteria, 27% of subjects failed to achieve a response, and the nadir IgM level exceeded 3000 mg/dl in 10% of responding subjects. Only 25/35 (71%) subjects presenting with adenopathy had reduction in adenopathy by CT, 4/7 (57%) subjects presenting with splenomegaly had reduction in spleen size, and the bone marrow response was usually incomplete (median reduction in bone marrow lymphoplasmacytoid cell percentage from 60% to 25%). In the initial report of this study, 2 of 7 (29%) of subjects with wild-type *MYD88* (*MYD88*^{WT}) by, were reported to have achieved a major response to ibrutinib; however, a subsequent report (Treon et al 2015b) noted that activating non-MUT mutations were found in both responding patients. Therefore, to date, major responses have not been reported in patients with wild-type *MYD88* WM. Of adverse events (AEs) potentially associated with ibrutinib treatment, Grade 2 or greater bleeding occurred in 6% of patients and atrial fibrillation was reported in 5% of patients. Six percent of patients discontinued treatment due to adverse events and dose reduction due to adverse events occurred in 11% of patients. In addition, 52 cases of ventricular tachyarrhythmia were reported in post-marketing settings of which the role of ibrutinib could not be ruled out in 2 cases. (EMA CHMP scientific conclusions for ibrutinib, 2017).

Zanubrutinib is a novel second-generation, potent, specific and irreversible BTK inhibitor. In the ongoing first-in-human Phase 1 study of zanubrutinib (BGB-3111-AU-003) in subjects with advanced B-cell malignancies, as of 03 November 2017, a total of 67 subjects with WM were enrolled in the study. All 67 subjects with WM were fully evaluable for safety and 51 subjects were evaluable for efficacy. The median follow-up in these patients was 15.5 months (0.1 to 37.6 months). No subjects had CR, 43% had very good PR (VGPR), and 37% had PR, for a major response rate (CR+VGPR+PR) of 80%. Preliminary gene sequencing data was available for all 51

patients evaluable for efficacy and suggests a high frequency of deep responses in patients with *MYD88^{MUT} WM*, with 16 of 30 (53%) *MYD88^{MUT}* WM patients achieving VGPR (Tam et al 2018).

Zanubrutinib was well tolerated across histologies and dosages. As of 15 September 2017, the most common (≥ 10%) treatment-emergent adverse events (TEAEs) for 58 subjects with WM were upper respiratory tract infection (39.7%); contusion (32.8%); constipation (20.7%); diarrhea (19.0%); cough (15.5%); nausea, back pain, headache, anemia, urinary tract infection (13.8% each), and rash (12.1%). Of the 58 evaluable subjects with WM, 6 subjects (10.3%) discontinued BGB- 3111 due to adverse events (AEs). No deaths were considered related to treatment. Refer to the Investigator's Brochure (IB) for more detailed information on zanubrutinib.

Zanubrutinib was designed to be a more specific inhibitor of the Bruton's tyrosine kinase than ibrutinib. Preclinical data in cell lines and primary patient samples show specific BTK inhibition with less inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2 and TEC than the first-generation BTK inhibitor ibrutinib. We hypothesize that this improved selectivity may result in a better safety profile than ibrutinib. Based on safety data of zanubrutinib above we perceive the risk of taking zanubrutinib to be similar or superior to those of ibrutinib and the benefit to be potentially greater. However, to minimize the risks associated with BTK inhibitors we have put rules in place. To minimize the risk of bleeding, subjects will hold study drug for 3 to 7 days pre- and post- surgery depending on the type of surgery and the risk of bleeding. Subjects will be closely monitored for infection and drug will be held and may be subsequently reduced, depending on recurrence, in the event of Grade 3/4 thrombocytopenias associated with significant bleeding as well as grade 4 thrombocytopenias lasting > 10 days, Grade 4 neutropenia (lasting > 10 days despite use of growth factors), and ≥ Grade 3 febrile neutropenia. Furthermore, study drug will be held for any ≥ Grade 3 bleeding, and permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in gastrointestinal [GI] bleed) and the risk of a re-bleed is deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should **not be** resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anti-coagulation or anti-platelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor. Subjects will be monitored for these adverse events.

We hypothesize that zanubrutinib will have sustained tissue penetration that may result in a deeper response than ibrutinib. Twice-daily zanubrutinib dosing results in high plasma exposure of zanubrutinib. Close to 100% sustained BTK occupancy was found in studies where paired patient

lymph node biopsies and blood samples were examined suggesting a deep tissue penetration of the drug. Phase 1 clinical data presented at the European Hematology Association meeting support this hypothesis. With a median follow up of 15.5 months (range, 0.1-37.6), an overall response rate of 92% (47 of 51), a major response rate of 81% (41 of 51), and a VGPR in 43% (22 of 51) of subjects with WM (Tam et al, 2018). To test these hypotheses more formally we have designed this head to head Phase 3 study to compare the efficacy and safety of zanubrutinib to ibrutinib.

2 OBJECTIVES

2.1 Primary Objective (Cohort 1)

- To compare the efficacy of zanubrutinib vs ibrutinib in subjects with *MYD88*^{MUT} WM

2.2 Secondary Objectives (Cohort 1)

- To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib vs ibrutinib in subjects with *MYD88*^{MUT} WM
- To evaluate safety and tolerability of zanubrutinib versus ibrutinib in subjects with *MYD88*^{MUT} WM, as measured by the incidence and severity of adverse events according to the National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) v4.03.

2.3 Exploratory Objectives

[redacted]

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is the proportion of subjects in Cohort 1 achieving either CR or VGPR, as determined by independent review committee (IRC) using an adaptation of the response criteria updated at the Sixth IWWM (Owen et al. 2013 and NCCN Guidelines, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia 2015: v2).

3.2 Secondary Endpoints

Efficacy (Cohort 1):

- Major response rate (MRR) as assessed by the IRC, defined as the proportion of subjects achieving CR, VGPR, or PR
- Duration of response (DOR) as assessed by the IRC, defined as the time from first determination of response (CR, VGPR or PR) (per modified IWWM criteria) until first documentation of progression (per modified IWWM criteria) or death, whichever comes first
- Rate of CR or VGPR as assessed by the Investigator
- DOR as assessed by the Investigator, defined as the time from first determination of response (CR, VGPR or of PR) (per modified IWWM criteria) until first documentation of progression (per modified IWWM criteria) or death, whichever comes first
- Progression-free survival (PFS) as assessed by the IRC, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first
- PFS as assessed by the Investigator, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first
- Resolution of treatment-precipitating symptoms, defined as the absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment
- Anti-lymphoma effect, defined as any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or splenomegaly by CT scan, at any time during the course of study treatment

Safety (Cohort 1)

- The incidence, timing, and severity of treatment-emergent AEs (TEAE) according to NCI-CTCAE v.03

3.3 Exploratory Endpoints

[redacted]

4 STUDY DESIGN

4.1 Summary of Study Design

This is a Phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors zanubrutinib and ibrutinib in subjects with Waldenström's Macroglobulinemia (WM) who require therapy according to the consensus panel criteria from the Seventh International Workshop on Waldenström's macroglobulinemia (Dimopoulos et al 2014). Subjects may be treatment-naïve (TN) or have relapsed or been refractory to prior therapy. Relapsed means a subject previously achieved a CR or VGPR/PR but after a period of 6 months or more showed progressive disease. Refractory means a subject experienced prior treatment failure or disease progression within 6 months of therapy initiation. Subjects with no prior therapy (TN) will comprise no more than 20% of the study analysis set in Cohort 1. The study is composed of an initial Screening Phase (up to 35 days), a Treatment Phase, and a Follow-up Phase. The study schema is presented in Figure 1.

Approximately 210 subjects will be enrolled on the study. All subjects enrolled on the study will have the *MYD88* gene sequenced by a central laboratory using the baseline bone marrow. Approximately one hundred and eighty-eight WM subjects (150 relapsed/refractory subjects and approximately 38 treatment-naïve subjects) who have the $MYD88^{MUT}$ mutation, which is characteristic of WM and present in approximately 90% of cases, will be enrolled on to Cohort 1 and randomized to one of two treatment arms (Cohort 1; zanubrutinib treatment [Arm A] or ibrutinib treatment [Arm B]) in a 1:1 ratio using *CXCR4* mutational status ($CXCR4^{WHIM}$ vs. $CXCR4^{WT}$ vs missing) and number of prior lines of therapy for WM (0 vs. 1-3 vs. >3 prior therapies) as stratification factors. Subjects found to have $MYD88^{WT}$ by gene sequencing, which is estimated to be present in approximately 10% of enrolled subjects, will be enrolled to Cohort 2 and will receive zanubrutinib treatment on a third, non-randomized study arm (Arm C). This non-randomized arm is aimed to evaluate the efficacy of zanubrutinib in $MYD88^{WT}$ WM subjects, among whom suboptimal efficacy has been observed (i.e., shorter median survival and lower MRR and CR/VGPR rates versus $MYD88^{MUT}$) when treated with ibrutinib. In addition, those subjects whose *MYD88* mutational status is missing or inconclusive will be assigned to Cohort 2, Arm C. Arm C will enroll approximately 22 subjects.

The primary efficacy analysis will be conducted approximately 12 months after the last relapsed/refractory subject in Cohort 1 is randomized. Tumor response will be assessed every cycle (every 4 weeks) for the first 48 weeks and then every 3 cycles thereafter by an independent review committee (IRC) according to an adaptation of the response criteria updated at the Sixth IWWM (Owen et al 2013; NCCN Guidelines, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia 2015: v2). Serum IgM and M-protein levels will be measured at Screening, on Day 1 of every cycle for the first 48 weeks (12 cycles) then every 3 cycles thereafter. For subjects

with evidence of extramedullary disease (lymphadenopathy and/or splenomegaly) by computed tomography (CT) scan at baseline, assessment by CT scan will occur every 12 weeks (starting from C4D1) during the first 48 weeks (until C13D1), then every 24 weeks until PD or complete resolution of extramedullary disease. A CT scan is also required at the safety follow-up visit. Bone marrow will be assessed by aspirate and biopsy at Screening, after 12 cycles (C13D1), at time of suspected CR, and as clinically indicated.

Response assessments will occur in all subjects at the beginning of every cycle (every 4 weeks) starting from C2D1 during the first 12 cycles (48 weeks), and then every 3 cycles (every 12 weeks) thereafter e.g., C2D1, C3D1, etc. For those with extramedullary disease at baseline response assessments must occur in conjunction with CT scans until resolution of extramedullary disease. For response assessments that occur during cycles where a CT scan is not required then results from prior scans (up to 12 weeks/3 cycles during the first 48 weeks/12 cycles and up to 24 weeks/6 cycles thereafter) can be carried forward in those subjects with extramedullary disease at baseline. Quality of life (QOL) will be measured every 12 weeks during the first 48 weeks, and then every 24 weeks thereafter by the EORTC QLQ-C30 and EQ-5D in $MYD88^{MUT}$ WM subjects (Cohort 1).

All subjects will be followed for AEs for 30 additional days after the last dose of study drug. All treatment-related AEs and serious AEs (SAEs) will be followed until resolution or stabilization. Efficacy evaluations will continue until documented PD for subjects who discontinued for reasons other than PD.

Screening Phase: Screening evaluations will be performed within 35 days prior to the randomization, with the exception of a fresh bone marrow biopsy, which may be performed up to 42 days prior to randomization, as long as no intervening therapy has been administered. A fresh bone marrow aspirate is required for flow cytometry and the *MYD88* and *CXCR4* mutational analyses at Screening. If subject enrolls based on a bone marrow biopsy that was obtained within the 42 days of randomization, then a fresh bone marrow aspirate will still be required during the Screening period. Subjects who agree to participate will sign the informed consent form prior to any screening evaluations. Screening procedures are outlined in Table 3. Screening evaluations can be repeated within the screening period.

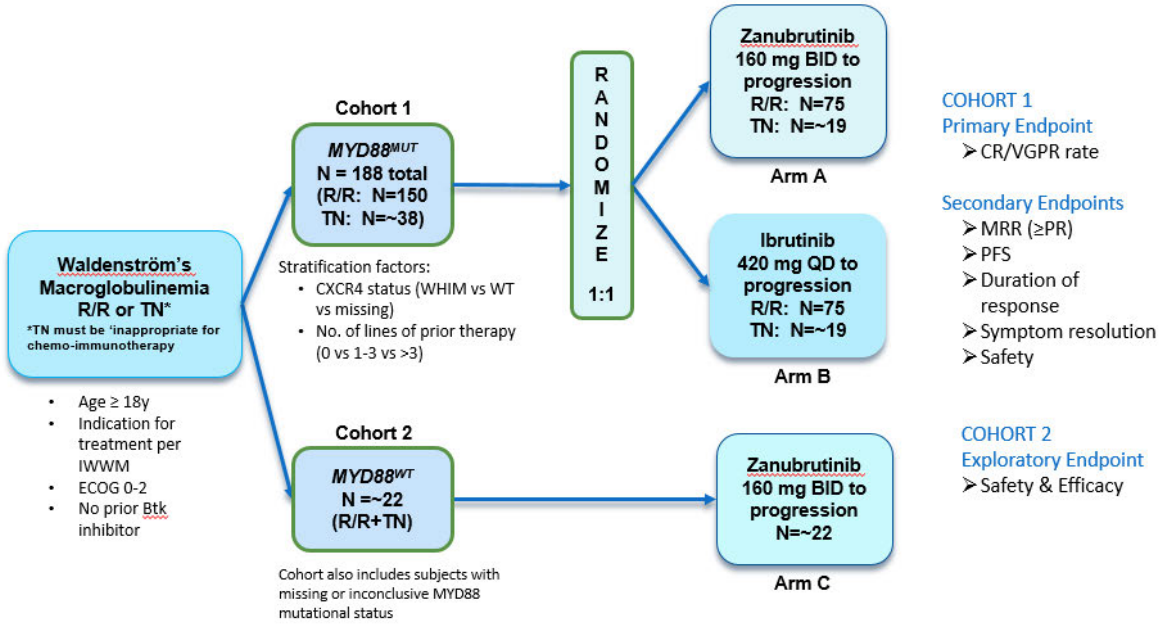
Treatment Phase: Subjects will be assigned to either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT/\text{missing}}$) based on the mutational status of the *MYD88* gene. Cohort 1 subjects will be randomized using an Interactive Response Technology (IRT) system by the status of stratification factors to receive the first dose of zanubrutinib or ibrutinib at Cycle 1 Day 1. Cohort 2 subjects ($MYD88^{WT/missing}$) will be assigned by the IRT to receive zanubrutinib. Subjects randomized to Arm A will take 160 mg (80 mg x 2 capsules) of zanubrutinib PO BID. Subjects randomized to Arm B will take 420 mg (140 mg x 3 capsules, or in other applicable dose forms) of ibrutinib PO QD. Subjects assigned to Cohort 2 (Arm C) will take zanubrutinib 160 mg (80 mg x 2 capsules) PO BID.

All subjects will continue to be treated and followed by the defined schedules in Table 3 for IgM, radiologic assessments and bone marrow, etc. until PD, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of treatment duration or the study is terminated by the sponsor, whichever comes first. A treatment cycle consists of 28 days.

Follow-up Phase: In all study arms, subjects will return approximately 30 days after the last dose of study drug for Safety Follow-up Visit(s) for the collection of AEs and SAEs that may have occurred after the subject discontinued from the study. For subjects that had extramedullary disease at baseline, a CT scan is also required at the Safety Follow-up Visit. All treatment-related SAEs will be followed until resolution or stabilization. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. Efficacy evaluations will continue until documented PD. If study drug is discontinued due to reasons other than PD, serum IgM and M-protein levels will continue to be followed every 12 weeks while other efficacy evaluations will be followed as per investigator's discretion. Efficacy assessments will be continued, as per protocol, until PD, withdrawal of consent, death, lost to follow-up, end of study or study termination by sponsor, whichever occurs first. Follow-up will continue to occur even though a subject may have started a new anticancer therapy after the last dose of study drug. For full efficacy assessment schedules, please refer to Section 7.3 and Table 3. Subjects will be followed for survival and further anticancer therapy information after progression of disease via phone contact (with the subject's guardian, if applicable) every 12 weeks until study end.

Post Study: Subjects assigned to Arms A and C (zanubrutinib) who, in the opinion of the investigator, continue to benefit from zanubrutinib or ibrutinib at study closure may continue treatment with zanubrutinib by enrolling on the zanubrutinib Long Term Extension Study. This study is a rollover study for subjects who wish to continue receiving zanubrutinib.

Figure 1. Schema for Study BGB-3111-302



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. Subjects must either have relapsed/refractory disease OR be treatment naïve and considered by their treating physician to be unsuitable for standard chemoimmunotherapy regimens.
    - For subjects who have received no prior therapy for WM: "Unsuitable" for treatment with a standard chemoimmunotherapy regimen must be a physician-determined status based on co-morbidities and risk factors. Physicians will need to provide and document organ system(s) and specific reason(s) for subject being considered unsuitable. Patient preference does not meet the eligibility requirement for a treatment-naïve subject to be unsuitable for treatment with a standard chemoimmunotherapy regimen
2. Meeting at least one criterion for treatment according to consensus panel criteria from the Seventh International Workshop on Waldenström's Macroglobulinemia (Dimopoulos et al 2014, detailed in Table 4, Section 7.2)
3. Measurable disease, as defined by serum IgM level > 0.5 g/dL
4. Age ≥ 18 years old
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
6. Adequate bone marrow function defined as:
    - Neutrophils ≥ 0.75 x 10^9/L, independent of growth factor support within 7 days of study entry
    - Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of study entry
7. Creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]) based on ideal body mass (EMA 2014; FDA 2010)
8. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN)
9. Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome)
10. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Subjects with factor inhibitors that prolong PT/aPTT without

increasing the bleeding risk or those with lupus anticoagulant or acquired von Willebrand's syndrome due to WM may be enrolled after discussion with the Medical Monitor or designee.

11. Subjects who relapse after autologous stem cell transplant are eligible if they are at least 3 months after transplant, and are eligible after allogeneic transplant if they are at least 6 months post-transplant. To be eligible after either type of transplant, subjects should have no active infections or in the case of allogeneic transplant relapse, no active acute graft versus host disease (GvHD) of any grade, and no chronic GvHD other than mild skin, oral, or ocular GvHD not requiring systemic immunosuppression.
12. Female subjects of childbearing potential and non-sterile males must practice highly effective methods of birth control initiated prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug. These methods include the following:
    - A barrier method of contraception (including male and female condoms with or without spermicide) plus one of the following hormonal contraceptives
        - Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
            - Oral, intravaginal or transdermal
        - Progestogen-only hormonal contraception associated with the inhibition of ovulation
            - Oral, injectable, implantable
        - An intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for 90 days after the last dose of study drug). Total sexual abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of

abstinence for the duration of exposure to the investigational medicinal product (IMP), and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above.

13. Life expectancy of > 4 months
14. Able to provide written informed consent and can understand and comply with the requirements of the study

5.2 Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

1. Prior exposure to a BTK inhibitor.
2. Evidence of disease transformation at the time of study entry.
3. Corticosteroids given with antineoplastic intent within 7 days, or chemotherapy, targeted therapy, or radiation therapy within 4 weeks, or antibody-based therapy within 4 weeks of the start of study drug.
4. Major surgery within 4 weeks of study treatment.
5. Ongoing toxicity of ≥ Grade 2 from prior anticancer therapy (except for alopecia, absolute neutrophil count [ANC] and platelets). For ANC and platelets, please follow inclusion criteria #6 [neutrophils] and [platelets]).
6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
7. Currently active, clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease (congestive heart failure) as defined by the New York Heart Association (NYHA) Functional Classification, or history of myocardial infarction within 6 months of screening.
8. QTcF prolongation (defined as a QTcF > 480 msec).
9. Active, clinically 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. Uncontrolled active systemic infection or recent infection requiring parenteral anti-microbial therapy that was completed ≤ 14 days before the first dose of study drug.
12. Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or hepatitis C infection as follows:
    a) Presence of hepatitis B surface antigen (HbsAg) or anti-hepatitis core antibody (anti-HBc). Patients with presence of anti-HBc, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable and if they are willing to undergo monthly monitoring for HBV reactivation.
    b) Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV ribonucleic acid (RNA) is undetectable.
13. Pregnant or lactating women.
14. Any life-threatening illness, medical condition, organ system dysfunction, need for profound anticoagulation, or bleeding disorder, which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk.
15. Inability to comply with study procedures.
16. At time of study entry, taking any medications which are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers.
17. At time of study entry, taking warfarin or other vitamin K antagonists.
18. Known CNS hemorrhage or stroke within 6 months prior to study entry.
19. CNS involvement by WM. Patients with a previous history of CNS involvement must undergo magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology studies to document no evidence of CNS disease prior to study entry.
20. History of intolerance to the active ingredients or other ingredients of either zanubrutinib or ibrutinib.

6 STUDY TREATMENT PHASE AND FOLLOW-UP PHASE

6.1 Study Treatment and Dose Rationale

Subjects randomized to Arm A or assigned to Arm C will receive zanubrutinib 160 mg (80 mg x 2 white capsules) PO BID. The dose of 320 mg total daily, given as divided dose of 160 mg PO BID was selected as the recommended Phase 3 dose based on PK/PD data, sustained target occupancy, high rates of objective response in multiple histologies, and a favorable safety and tolerability profile. Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all subjects starting at 40 mg zanubrutinib in the Phase 1/2 study, while occupancy in lymph node tissue was assessed only at 160 mg BID and 320 mg daily. At the 160 mg BID dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across 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 dose; which shows a high level of activity without compromise of the tolerability profile as compared to lower doses of zanubrutinib.

Subjects randomized to Arm B will receive ibrutinib 420 mg (140 mg x 3 capsules, or in other applicable dose forms) PO QD as per prescribing information. For example, as available, one 420 mg tablet or 140 mg x 3 tablets.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

Zanubrutinib capsules will be provided in a child-resistant high-density polyethylene (HDPE) bottle with induction seal and bottle label. Commercial supplies of ibrutinib will be provided by the sponsor or via local procurement by the site. In the case of local procurement, the cost for provision of ibrutinib may be covered by a patient's insurance or via reimbursement by the sponsor. The contents of study treatment labels will be in accordance with all applicable local regulatory requirements.

All study treatments will be consistent with those described in the Pharmacy Manual for this study.

6.2.2 Handling and Storage

Interactive Response Technology (IRT) system will be used for drug supply management. The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The Investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledgment receipt of all study drug shipments. All study drug must be stored in a secure area

with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug-specific requirements. The study drug must be kept at the condition as specified on the labels. Zanubrutinib bottles must be stored at room temperature 15ºC to 30ºC. For ibrutinib, each country should follow the storage condition instructions on the local drug label. Study drug must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug.

6.2.3 Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel by reviewing the patient diary and information provided by the subject and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed All subjects enrolled in the study will be provided with patient diaries. The subject is responsible for maintaining the patient diary. The subject will record the number of capsules (or in other dose forms as applicable, eg, tablets) taken and if any were missed. The site personnel responsible for drug accountability will record the quantity of drug dispensed and quantity of drug returned at periodic visits by the patient, or at any cycle visit if dosing non-compliance is suspected. The patient diaries and the pharmacist record of drug dispensation will be assessed by the Investigator/study personnel at each visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by subjects, if applicable.

6.2.4 Disposal and Destruction

At appropriate times during the conduct of the study or after completion of the study, all unused zanubrutinib and ibrutinib will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.3 Subject Numbering and Treatment Assignment

6.3.1 Subject Numbering and Screening

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned by the IRT system when the subject is screened in the study. Subject number 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.

Repeating the screening procedures or tests within the original screening window is allowed if the subject did not previously meet the inclusion and exclusion criteria. A new informed consent is not required and the subject shall maintain the same subject number as originally assigned. Within the screening window, a failed screening test can only be repeated one time.

The Investigator is responsible for ensuring that the patient meets the eligibility criteria for this study. An eligibility packet which contains checklist of the inclusion/exclusion criteria and scanned copies of subject's source data/documents will need to be provided to the Medical Monitor or designee for review during the screening period. Medical Monitor or designee will confirm whether the subject is eligible for the study and confirmation will be sent to the site. Subject can not be randomized until confirmation from the Medical Monitor or designee is received.

6.3.2 Treatment Assignment

After a subject has completed all screening procedures and meets the eligibility criteria, study center personnel can enroll the subject. Based on *MYD88* gene sequencing, the subject will be enrolled into either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT}$). Those subjects with either missing or inconclusive *MYD88* gene sequencing results will be assigned to Cohort 2 by default.

Approximately 210 subjects will be enrolled into the study. Aproximately 188 subjects from Cohort 1 ($MYD88^{MUT}$), including 150 subjects with relapsed refractory WM and approximately 38 subjects with treatment-naïve WM, will be randomized in a 1:1 ratio using the IRT system to receive either zanubrutinib (Arm A) or ibrutinib (Arm B). Stratification factors include *CXCR4* mutational status ($CXCR4^{WHIM}$ vs. $CXCR4^{WT}$ vs missing) and the number of prior lines of therapy for WM (0 vs. 1-3 vs. >3). A computer-generated randomization list including stratification factor values and treatment arm assignments will be produced, reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report (CSR) for this study. Subjects from Cohort 2 (approximately 22 subjects who are $MYD88^{WT/\text{missing}}$) will be assigned to Arm C using IRT to receive zanubrutinib capsules.

Cohort 2 assignment and stratified randomization of Cohort 1 will be performed centrally by the IRT system on or immediately prior to Cycle 1 Day 1. The investigator or his/her delegate will call the IRT after confirming that the subject has fulfilled all the eligibility criteria. At randomization, the IRT will assign each subject a unique number. This unique patient number will be used to identify the patient in the electronic data capture (EDC) system and other data sources. The randomization list will be kept by the IRT vendor in their secure system and will not be accessible to the study center, responsible (or designee) monitors, project statisticians, or to the project team at BeiGene. The time from randomization of the subject to the initiation of therapy should be no more than 5 days.

6.3.3 Treatment Blinding

This is an open-label study. The IRC will be blinded to study treatment. The independent data monitoring committee (DMC) will not be blinded.

6.4 Dosage and Administration

Zanubrutinib or ibrutinib will be dispensed by the study center personnel to subjects at scheduled study visits to ensure adequate drug supply for administration at home throughout the Treatment Phase. The investigator is to instruct the subject to take the study drug exactly as prescribed and at the same time each day of dosing. Subjects will be requested to bring their unused medication including empty bottles to the center at each visit. All dosages prescribed and dispensed to the subject and all dose changes including reason for dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

Subjects randomized or assigned to zanubrutinib (Arms A and C) will be instructed to take 160 mg (80 mg x 2 capsules) orally with a glass of water twice a day at approximately the same time each day. The time difference between two consecutive doses should be a minimum of 8 hours. Subjects randomized to ibrutinib (Arm B) will be instructed to take 420 mg (140 mg x 3 capsules or in other applicable dose forms) orally with a glass of water, once a day at the approximately same time each day.

Zanubrutinib (Arms A and C) or ibrutinib (Arm B) should be taken within 5 days from the time of subject randomization.

Subjects are not required to fast before or after the administration of either zanubrutinib or ibrutinib. Zanubrutinib or ibrutinib will be taken as prescribed from Cycle 1 Day 1 until PD, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or termination of the study by the sponsor, whichever comes first. Zanubrutinib capsules or ibrutinib in any applicable dose forms should not be opened, broken, or chewed at any time.

In subjects undergoing pharmacokinetics (PK) blood sampling, study drug administration for subjects randomized or assigned to Arms A and C (zanubrutinib) will occur on the specified days at the center after the pre-dose blood sampling has occurred under the supervision of the investigator or his/her designee. The investigator or his/her designee must instruct the subject not to self-administer the study drug prior to the office visit on those days.

Subjects on Arms A and C (zanubrutinib) should be instructed that if a dose of the study drug is not taken at the scheduled time, they should skip the study drug if the time to next dose is 8 hours or less, and return to normal dosing with next dose. If subjects vomit after taking the capsules, they should not repeat that dose.

Subjects on Arm B (ibrutinib) should be instructed that if a dose of the study drug is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to normal dosing the next day, or to take ibrutinib according to local prescribing guidelines. The patient should not take extra capsules (or in other applicable dose forms) to make up the missed dose. If subjects vomit after taking the capsules, they should not repeat that dose.

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. AEs associated with an overdose of study drug should be recorded as an AE in the patient's chart and on the appropriate eCRF. Any SAEs associated with an overdose are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 9.2.2. There is no specific antidote for either zanubrutinib or ibrutinib. In an event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

6.5 Dose Interruption and Modification

The guidelines set forth in Table 1 should be followed for dose interruption or modification of zanubrutinib or ibrutinib for hematologic (Section 6.5.1) or non-hematologic (Section 6.5.2) toxicities based on investigator assessment of study drug relatedness.

Study drug may be held for a maximum of 2 consecutive cycles and restarted upon resolution of toxicity and per investigator discretion. If, in the investigator's opinion, it is in the subject's best interest to restart treatment after being held for more than 2 consecutive cycles, then written approval must be obtained from the Sponsor's Medical Monitor or designee. More than one study drug hold is allowed.

Table 1. Zanubrutinib and Ibrutinib Dose Reduction Steps

Toxicity Occurence	**Dose Level**	**Zanubrutinib Dose (Arms A & C) (Starting dose = 160 mg BID)**	**Ibrutinib Dose (Arm B) (Starting dose = 420 mg QD)**
First	0 = starting dose	Restart at 160 mg BID	Restart at 420 mg QD
Second	-1 dose level	Restart at 80 mg BID	Restart at 280 mg QD
Third	-2 dose level	Restart at 80 mg QD	Restart at 140 mg QD
Fourth	Discontinue Study Drug	Discontinue zanubrutinib	Discontinue ibrutinib

BID=twice daily; QD=once daily

6.5.1 Dose Modifications for Hematologic Toxicity for Zanubrutinib

For zanubrutinib, dosing will be held for hematologic toxicity suspected to be related to study drug treatment under any of the following conditions:

- Grade 4 neutropenia (lasting >10 days despite the use of growth factors)
- Grade 4 thrombocytopenia (lasting >10 days)
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 3 thrombocytopenia associated with significant bleeding

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

6.5.2 Dose Modifications for Non-Hematologic Toxicity for Zanubrutinib

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

Zanubrutinib should be held for any ≥ Grade3 bleeding. The drug should be permanently discontinued for any related ≥ 3 Grade hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in GI bleed) and the risk of a re-bleed is deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should **not be** resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anti-coagulation or anti-platelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor.

6.5.3 Dose Modifications for Zanubrutinib when Co-adminstered with Strong/Moderate CYP3A Inhibitors/Inducers

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 3 and Table 2 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification guidelines in Table 2. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Table 2. Dose Modification for Zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	**Strong CYP3A inhibitor** (eg. ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	**80 mg once daily**
	Moderate CYP3A inhibitor (eg. erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, and grapefruit products)	**80 mg twice daily**
Induction	Strong CYP3A inducer (eg. carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg. bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

6.5.4 Dose Modifications for Ibrutinib

For dose modification of Ibrutinib, local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) should be followed throughout the study. The major dose modifications for ibrutinib are described below:

Ibrutinib should be interrupted for any new onset or worsening ≥ Grade 3 non-hematologic toxicities, ≥ Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib therapy may be re-initiated at the starting dose. If the toxicity recurs, drug dose will be reduced to Dose Level -1 (280 mg orally QD). A second dose reduction to Dose Level -2 (140 mg orally QD) may be considered as needed. If these toxicities persist or recur following 2 dose reductions, the subject will be discontinued for study treatment.

As with zanubrutinib, ibrutinib should be interrupted for any ≥ Grade3 bleeding. The drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (e.g. gastric ulcer resulting in GI bleed) and the risk of a re-bleed is deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug should be held and the risk of rebleeding should be assessed. If the risk of rebleeding is deemed unacceptable, which is expected in the majority of cases, the study drug should be permanently discontinued. Study drug should **not be** resumed unless event resolution has been demonstrated by CT scans or MRI, the risk of rebleeding is deemed low, and the patient does not have a need for concurrent anti-coagulation or anti-platelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption can only occur after a discussion and approval by the study medical monitor.

Use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used.

As described in Section 6.6.2, concomitant use of ibrutinib with strong and moderate CYP3A4 inhibitors should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, ibrutinib dose must be reduced or withheld temporarily (7 days or less). Ibrutinib dose must be reduced when administered with moderate CYP3A inhibitors. Refer to the local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) for specific instructions on dose modifications with these inhibitors.

For patients with mild hepatic impairment (Child-Pugh Class A) and patients with moderate hepatic impairment (Child-Pugh Class B), refer to the local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) for specific instructions on dose modifications of ibrutinib.

It is not recommended to administer ibrutinib to patients with severe hepatic impairment (Child-Pugh Class C).

6.6 Concomitant Medications and Non-Drug Therapies

6.6.1 Permitted Medications

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

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

Corticosteroid courses of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition.

Bisphosphonates can be coadministered with zanubrutinib.

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

6.6.2 Prohibited Medications

Subjects should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement) while on treatment in this study. Other anticancer therapy, experimental therapy and radiotherapy are prohibited and should not be administered until PD (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the study drug.

Any anticancer chemotherapy, immunotherapy, corticosteroids given with antineoplastic intent, experimental therapy, and radiotherapy are prohibited.

Corticosteroid courses of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition. The chronic use of corticosteroids at doses equivalent to adrenal replacement (2.5 mg to 7.5 mg prednisone) is prohibited without previous discussion with and approval from the Medical Monitor or designee.

Use of warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil or supplements and vitamin E preparations should be avoided.

Use of preparations containing St. John’s Wort should be avoided.

The primary metabolic pathway for ibrutinib involve the CYP3A isoform. Administration of ibrutinib with strong CYP3A inhibitors or CYP3A inducers should be avoided and consider using alternative agents. In addition, star fruit, pomegranate and grapefruit and their juices and Seville oranges (bitter oranges) should be avoided since they are known to affect the CYP3A pathway.

Co-administration of strong or moderate CYP3A4 inhibitors with ibrutinib may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased ibrutinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors/inducers should be avoided.

If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the ibrutinib dose or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A4 inhibitor must be used, reduce ibrutinib treatment for the duration of the inhibitor use. Refer to the local prescribing guidelines (Prescribing Information or Summary of Product Characteristics) for specific guidelines on dose modifications.

Refer to Appendix 3 for examples of strong and moderate CY3A4 inhibitors or inducers. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

6.6.3 Medications to be Used with Caution

Ibrutinib is metabolized to a minor extent by CYP2D6. Other than strong or moderate CYP3A4 inhibitor and inducers, CYP 450 enzyme class drug is not restricted in ibrutinib prescribing information Zanubrutinib is primarily metabolized by CYP3A (see Section 1.3.4),

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Table 2 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table in Table 2. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Based on in vitro data, zanubrutinib may have the potential to affect the human isoenzymes CYP2C8 activity (Section 1.3.2). A clinical drug-drug interaction study (Study BGB-3111-108) indicated that zanubrutinib does not inhibit CYP2C9, however, is a mild inducer of CYP3A4 and CYP2C19 (Section 1.3.4). Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) or CYP2C8 should be used with caution (Appendix 4), as zanubrutinib may decrease the plasma exposures of these drugs. Because ethinylestradiol (a key ingredient in a variety of combined oral contraceptives) is partly metabolized

by CYP3A4, patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well (see Section 5.1).

Repeated dosing of zanubrutinib increased exposure of digoxin (P-gP substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max} .(Section 1.3.4). The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

6.6.4 Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment for either zanubrutinib or ibrutinib should be held for 3 to 7 days pre- and 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 End of Treatment

All subjects, regardless of reason for discontinuation of study treatment will undergo 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 the eCRF.

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

- Disease progression
- Adverse event(s)
- Subject withdrew consent
- Investigator Decision
- Other

Subjects may voluntarily withdraw consent from treatment at any time. Subjects will continue into the Follow-up Phase if subject withdraws consent from the Treatment Phase.

Subjects who are continuing to receive benefit from zanubrutinib after disease progression may remain in the study upon discussion with the Medical Monitor or designee. These subjects that remain in the study will continue to follow the required assessments during the treatment phase.

6.8 Follow-Up Phase

6.8.1 Safety Follow-Up

All subjects who discontinue study drug and agree to a follow-up visit will have a safety follow-up visit approximately 30 days after the last dose of study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the study treatment. All treatment-related SAEs will be

followed until resolution or stabilization. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. For subjects that had extramedullary disease at baseline, a CT scan is also required at this visit. 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.

6.8.2 Efficacy Follow-Up

Subjects who are discontinued from study drug for any reason other than PD will be followed every 12 weeks (±14 days) until disease progression, withdrawal of consent, death, lost to follow-up, end of study or study termination by sponsor, whichever occurs first. Follow-up will continue to occur even though a subject may have started a new anticancer therapy after the last dose of study drug. IgM will continue to be followed every 12 weeks while other efficacy evaluations will be followed as per investigator's discretion.

For full efficacy assessment schedules, please refer to Section 7.3 and Table 3. If the subject refuses to return for these visits or is unable to do so, every effort should be made to contact them or subject's guardian by telephone to determine the subject's disease status and survival.

6.8.3 Survival Follow-Up

Subjects will be followed for survival and further anticancer therapy information post progression via phone contact (with the subject's guardian, if applicable) every 12 weeks (±14 days) as per Section 4.1 until study end.

6.9 End of Study

Premature discontinuation from the study (including all follow-up visits) will occur under the following circumstances:

- Subject withdrew consent
- Lost to follow-up
- Death
- Study termination by sponsor
- Other

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

Subjects lost to follow-up should be recorded as such in the eCRF. 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, e.g., 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

	Pre−treatment	Treatment Each cycle = 28 days				End of Treatment	Follow-up	
	Screening[1]	Cycle 1	Cycle 2	C3-13	C16, C19, C22+ (every 3 cycles) Subjects must come every cycle for CBC, study drug, and patient diary review	EOT	Safety Follow-up Visit [18]	Follow-up (every 12 weeks)
Day of cycle	−35 to -1	D1	D1±4	D1±4	D1±7	≤7 days after last dose	30 days after last dose	≤ 14 days
Informed consent	X [2]							
Inclusion/exclusion criteria	X [3]							
Demography	X [4]							
Medical/surgical history/current medical conditions	X [5]							
WM diagnosis	X [6]							
Prior antineoplastic therapy	X							
Randomization via IRT	X [7]							
12-lead ECG [8]	X	X	X	X (Every 4 cycles)	X (Every 4 cycles)	X		
ECHO/MUGA	X [9]							
ECOG performance status	X	X	X	X	X	X	X	
Height (cm)	X							
Weight (kg) [10]	X	X	X	X	X	X	X	
Vital signs / physical examination / B symptoms assessment/ review and documentation of baseline reasons for treatment initiation and review for arrhythmia signs/symptoms [10]	X	X	X	X	X	X	X	
Complete Blood Count (CBC) [11]	X	X	X	X	X (every cycle)	X		
Chemistry and β2-microglobulin [11]	X	X	X	X	X	X		
Coagulation [11]	X							
Urinalysis [11]	X	X	X	X	X	X		

Table 3. Study Assessments and Procedures Schedule (continued)

	Pre-treatment	Treatment Each cycle = 28 days				End of Treatment	Follow-up	
	Screening[1]	**Cycle 1**	**Cycle 2**	**C3-13**	**C16, C19, C22+ (every 3 cycles) Subjects must come every cycle for CBC, study drug, and patient diary review**	**EOT**	**Safety Follow-up Visit** [18]	**Follow-up (every 12 weeks)**
Day of cycle	-35 to -1	D1	D1±4	D1±4	D1±7	≤7 days after last dose	30 days after last dose	≤ 14 days from last visit
Quantitative serum immunoglobulins[11] (starting at end of Cycle 1/start of Cycle 2)	X	X (pre-dose)	X	X	X	X		X[11]
Response Assessment[11]			X	X	X	X		X
Serum immunoelectrophoresis, with M-protein quantitation by densitometry (SPEP) and serum immunofixation[11]	X	X (pre-dose)	X	X	X	X		X[11]
Cold agglutinins[11]	X	*For any abnormal result, the abnormal test should be repeated every cycle for the first 48 weeks, then every 3 cycles, and at time of suspected CR. Once normalized, to be repeated every 3 cycles and at time of suspected CR*						
Cryoglobulin[11]	X							
Anti-MAG (myelin associated glycoprotein) [11]	X							
Serum viscosity[11]	X							
Iron, TIBC and Ferritin[11]	X							
Hepatitis B/C testing [11]	X	*Subj negative for HBsAg, HBcAb positive, and HBV DNA negative must undergo monthly HBV DNA screening by PCR. Subj positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA screening.*						
Pregnancy test (if applicable) [11]	X (within 7 days of randomization)	X (Day 1 and Day 28)	Every 4 weeks (Day 28 of each cycle)			Every 4 weeks (cycle) for at least 90 days after the last dose of study drug		
Pharmacokinetics [12]		X	X					
Study drug administration (zanubrutinib or ibrutinib) [13]		X	Continuous dosing in 28-day cycles (28-day ± 3 day cycles after C13) until PD, unacceptable toxicity, or withdrawal of consent					

Table 3. Study Assessments and Procedures Schedule (continued)

	Pre-treatment	Treatment Each cycle = 28 days				End of Treatment	Follow-up	
	Screening[1]	**Cycle 1**	**Cycle 2**	**C3-13**	**C16, C19, C22+ (every 3 cycles) Subjects must come every cycle for CBC, study drug, and patient diary review**	**EOT**	**Safety Follow-up Visit** [18]	**Follow-up (every 12 weeks)**
Day of cycle	-35 to -1	D1	D1±4	D1±4	D1±7	≤7 days after last dose	30 days after last dose	≤ 14 days from last visit
Biopsy for amyloidosis (e.g., Fat pad/bone marrow) [14]		At time of suspected CR only in subjects with known amyloidosis						
Bone marrow biopsy/aspiration[15]	X[15]	At 48 weeks (C13D1), at time of suspected CR, and as clinically indicated. *Optional bone marrow aspiration collection for correlative study in subjects with progressive disease*						
Imaging [16]	X	Every 12 weeks (starting C4D1) during the first 48 weeks (ending C13D1), then every 24 weeks (i.e., every 6 cycles) thereafter (±7 days)					X[16]	X[16]
QOL (EORTCQLQ-C30) and EQ-5D [17]	X	Every 12 weeks (starting C4D1) during the first 48 weeks (ending C13D1), then every 24 weeks (i.e., every 6 cycles) thereafter						
Brain CT/MRI scan with contrast	As clinically indicated							
Concomitant medications and medical resource utilization[17]	Throughout study							
AEs/SAEs[19]	Throughout study							
Antineoplastic therapies since discontinuation of study drug							X[20]	X[20]
Survival follow-up								X[20]
Patient diary[21]		X	X	X	X (every cycle)	X		

Abbreviations: AEs: adverse events; CBC: complete blood count; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECHO/MUGA; echocardiogram/Multiple Gated Acquisition scan; ECOG: Eastern Cooperative Oncology Group; EOT: End of Treatment; Ig: immunoglobulin; IRT: Interactive Response Technology; MRI: magnetic resonance imaging; PCR: polymerase chain reaction; QOL: quality of life; SAEs: serious adverse events; TIBC: total iron binding capacity; WM: Waldenström's Macroglobulinemia; X: to be performed

Windows: Days allowed for reschedule of an entire visit due to logistic reasons (e.g., Public Holidays)

Assessments scheduled on Cycle 1 Day 1 (C1D1) should be performed prior to the administration of the first dose of zanubrutinib or ibrutinib. Screening blood and urine tests performed within 72 hours of the first administration of study drug do not need to be repeated on C1D1. Please refer to Section 7.5 for the requirements of central or local analysis regarding blood laboratory assessments.

1. The center must register the subject at screening.in the IRT system.
2. Written informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
3. Screening evaluations will be performed and completed within 35 days of the randomization. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to C1D1. The investigator will review and ensure that the subject meets all of the inclusion and none of the exclusion criteria and that *MYD88* gene sequence has been assessed by central laboratory ($MYD88^{MUT}$, $MYD88^{WT}$, or indeterminant).
4. Demography includes gender, date of birth (or age), and race/ethnicity.
5. Relevant medical history (i.e., 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, includes background information such as history of disease and current disease status, staging (at time of diagnosis and at time of treatment), bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.
7. The center will utilize the IRT system for Cohort 1 to randomize subjects to Arm A or Arm B, or for Cohort 2 to assign subjects to Arm C in the trial upon completion of the all screening activities. Randomization of Cohort 1 can occur on or immediately prior to C1D1. The time from randomization of the subject to the initiation of therapy should be no more than 5 days.
8. Perform a 12-lead ECG in triplicate at Screening for all subjects. For subjects assigned to the zanubrutinib arm, perform a 12-lead ECG in triplicate at pre-dose (within 30 min prior to dose), 2 hours (± 30 min) post-dose on C1D1 and C2D1, and then continue to one 12-lead ECG in triplicate every 4 cycles thereafter [at C6D1, C10D1, etc] until EOT (this can be performed at either pre-dose or post-dose). For subjects assigned to the ibrutinib arm, perform a 12-lead ECG in triplicate at C1D1 and C2D1 and every 4 cycles thereafter (C6D1, C10D1 etc.) until EOT (this can be performed at either pre-dose or post-dose). Subjects should be in the semi-recumbent or supine position.
9. Perform ECHO/MUGA at the local lab at Screening, and when clinically indicated.
10. Physical examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, and temperature), weight, B symptoms examination, and review for arrhythmia signs/symptoms will be performed at the time points specified. In addition, baseline reason(s) for treatment initiation must be reviewed and documented at each visit. Symptoms that triggered treatment will be followed at, during, and end of treatment until resolutions. A complete physical exam includes assessments of cardiovascular, respiratory, and neurological systems as well as the examination of the abdomen, lymph nodes, spleen, skin, oropharynx and extremities. Clinical suspicion of PD at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B symptoms include unexplained weight loss > 10% over previous 6 months, fever (≥38°C), and/or drenching night sweats. The review for arrhythmia signs/symptoms for all subjects will be conducted by the Investigators by providing a questionnaire to be completed by all subjects enrolled in the study. These questions will include signs and symptoms of ventricular dysfunction (e.g., shortness of breath, dizziness, or fainting). The completed questionnaire will be provided back to the investigator for review and the Investigator will monitor the subjects at every clinic visit as part of the routine AE monitoring. Data collected at each visit (Day 1 of each cycle during the first 48 weeks [until C13D1], then every 3 cycles [every 12 weeks], and at EOT and Safety Follow-up Visits) will be recorded in the eCRF.).
11. Laboratory assessments include the following:
    a. Screening clinical laboratory assessments performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1. Screening quantitative serum immunoglobulin (IgG, IgM, IgA), β2-microglobulin and serum immunoelectrophoresis, with M-protein quantitation by densitometry (SPEP), performed within 14 days of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.
    b. Complete Blood Count is required to be performed every cycle (every 4 weeks) during the Treatment Phase. Clinical Chemistry and urinalysis tests will follow the same schedule to be performed at Screening, on every cycle (every 4 weeks) for the first 48 weeks and every 3 cycles (every 12 weeks) thereafter.
    c. Complete Blood Count includes red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils) and platelet count. In the event of neutropenia (absolute neutrophil count [ANC] < 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).

d. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, 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. The Screening β2-microglobulin, if performed within 14 days of the first administration of study drug, does not need to be repeated on C1D1.

e. Coagulation profile will be performed at Screening only includes prothrombin time (PT), which will also be reported as international normalized ratio (INR).

f. Quantitative serum immunoglobulins (IgG, IgM, IgA) and β2-microglobulin will be measured at Screening Visit, pre-dose on C1D1, on Day 1 of every cycle for the first 48 weeks through and including Day 1 of Cycle 13, then on Day 1 of every 3 cycles starting on Cycle 16 (C16, C19, C22 etc.). If a subject discontinues study drug due to reasons other than PD, the screening serum immunoglobulins (IgG, IgM, IgA) and β2-microglobulin will continue to be followed every 12 weeks. The Screening serum immunoglobulin (i.e.,ie, IgG, IgM, IgA) and β2-microglobulin, if performed within 14 days of the first administration of study drug, do not need to be repeated on C1D1. Response assessments will be documented every cycle (starting from C2D1) for the first 48 weeks (12 cycles) then every 12 weeks (3 cycles) thereafter as indicated in Section 7.3. Assessments will be based on physical examination (in cases in which organomegaly is present), laboratory evaluations, quantitative immunoglobulins and SPEP, radiologic assessment, and bone marrow studies. For response assessments during cycles when a CT scan is not required, the results of the most recent CT scan(s) may be used for the response assessment only if the prior scan date is within 12 weeks of the response assessment date during the first 48 weeks of the study and within 24 weeks of the response assessment date thereafter.

g. SPEP and serum immunofixation will be performed at Screening Visit, on Day 1 of every cycle for the first 48 weeks until Day 1 of Cycle 13 with the C1D1 sample drawn at pre-dose, then every 3 cycles starting on Cycle 16 (C16, C19, C22 etc.) and thereafter. The Screening serum immunoelectrophoresis, with M-protein quantitation by densitometry (SPEP), performed within 14 days of the first administration of study drug do not need to be repeated on C1D1.

h. Cold agglutinins, cryoglobulin; anti-MAG (myelin associated glycoprotein) and serum viscosity will be performed at Screening. 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 48 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. Of note, subjects that have cryoglobulinemia at Screening and confirmed by the central test should be tested for the presence of cryoglobulins at the local laboratory prior to C1D1. The C1D1 sample will serve as the baseline. The test for cryoglobulinemia should always be performed under warm conditions. The local laboratory should be used to test for cryoglobulinemia throughout the study to ensure that the same methodology is used throughout the study. In addition, serum immunoglobulins should be retested using the residual cryoglobulin blood sample, which is to be collected and processed under warm conditions at the local laboratory throughout the study. If serum immunoglobulins cannot be quantified, the serum immunoelectrophoresis sample will need to be re-collected, processed, and analyzed at the local laboratory under warm conditionsThese blood samples (cryoglobulin/serum IgM/SPEP/serum immunofixation) are to be collected and processed under warm conditions.

i. Iron, TIBC, and Ferritin will be performed at Screening only. If abnormal, iron supplementation should be provided per investigator's discretion prior to initiation of study treatment.

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

k. Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal (may be at investigator discretion except when urine protein ≥ 2+). Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated. All these tests will be performed in a local laboratory.

l. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at Screening within 7 days of randomization. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Cycle 1 Day 1, then on Day 28 of every cycle (which can be performed on Day 1 of the following cycle). Any female subject who is pregnant will not be eligible for the study. Urine or serum pregnancy tests must be continued every 4 weeks (cycle) for at least 90 days after the last dose of study drug. At the last dose of study drug, a serum pregnancy test is required (EOT). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

12. Pharmacokinetic samples will be collected from select subjects randomized to Arms A and C (zanubrutinib) at the following time points: pre-dose (within 30 min of dose), 2 hours (±30 min) post-dose and before subject discharge (3-6 h post-dose) on Cycle 1 Day 1 and Cycle 2 Day 1. The time of study drug administration on the day prior to Cycle 2 Day 1 must be recorded on the eCRF. Additionally, subjects who receive plasmapheresis (in Cycle 1 or Cycle 2 or beyond) will be evaluated for the effects of plasmapheresis on PK, including collection of additional PK samples immediately before the start of plasmapheresis, approximately an hour after the start of the procedure, and 30 min after the end of procedure (please also see Section 7.6.2). Subjects are recommended to receive zanubrutinib in the clinic on day of plasmapheresis and plasmapheresis is to commence between 2 to 3 hours (T_{max}) following zanubrutinib dosing.
13. Zanubrutinib and ibrutinib will be dispensed by the study center personnel on scheduled study visits, approximately every 4 weeks (every cycle), to ensure adequate drug supply for each cycle throughout the Treatment Phase. Subjects randomized to Arm A, or assigned to Arm C will receive zanubrutinib at a dose of 160 mg (80 mg x 2 white opaque capsules) PO BID. Subjects randomized to Arm B will receive ibrutinib at a dose of 420 mg (e.g.140 mg x 3 capsules). Zanubrutinib or ibrutinib will be administered on a 28-day cycle and will continue until PD, unacceptable toxicity or death, withdrawal of consent, or study terminated by sponsor 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 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.
14. Fat pad biopsy or biopsy of other relevant tissue (e.g., bone marrow) for subjects with a previous biopsy positive for amyloidosis will be collected at the time of suspected CR by IgM response.
15. Screening bone marrow biopsy samples is allowable within 42 days prior to randomization unless intervening therapy; however, a fresh bone aspirate must be collected during the Screening period for the flow cytometry and the mutation analyses. A bone marrow aspirate and biopsy must be performed for all subjects at 48 weeks, (C13D1), at time of suspected CR, and as clinically indicated. An aliquot of bone marrow specimen from Screening will be used for mutation analysis, including but not limited to *MYD88* and *CXCR4*. Optional bone marrow aspiration will be collected in subjects with progressive disease for studying the resistance mechanism. With Medical Monitor (or designee) approval, archival tissue from a prior bone marrow biopsy may be sent to the central lab for assessment of mutation status; this will be allowed only if the fresh bone marrow biopsy/aspirate result in an indeterminate mutation result by the central lab.
16. CT scans should encompass neck, chest, abdomen, pelvis and include oral and/or intravenous contrast. An MRI of the head is required if clinically indicated. An MRI may be used in place of CT for anatomic lesions which cannot be adequately visualized by CT or for subjects who cannot undergo CT (e.g., due to inability to take contrast). The CT portion of a PET/CT scan can also be performed. In Germany, an MRI may be used in place of CT in all subjects. However, in all cases the same modality should be used throughout the study. 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. For subjects with evidence of extramedullary disease (lymphadenopathy and/or splenomegaly) by CT scan at baseline, assessment by CT or scan will occur every 12 weeks starting on Day 1 of Cycle 4 (C7, C10 and C13 etc.) during the first 48 weeks, then every 24 weeks (C19, C25 etc.) starting on Cycle 19 until PD, resolution of extramedullary disease, or EOT, whichever comes first. Additionally, for subjects with extramedullary disease at baseline, a CT scan is also required at the safety follow-up visit. Unscheduled response assessments may be performed based on physical examination or laboratory findings, at the discretion of the investigator. CT scans for post treatment follow-up will be performed as per investigator's discretion for subjects discontinued due to the reasons other than PD**.**
17. In Cohort 1 (Arm A and Arm B only) quality of life (QOL) will be measured at C1D1 pre-dose (to avoid having subjects in Cohort 2 having to complete this at Screening) and every 3 cycles during the first 12 cycles then every 6 cycles thereafter throughout the study using the EORTC QLQ-C30, and EQ-5D. In addition, in Cohort 1, medical resource utilization will be recorded at each visit, including Screening and C1D1, including hospitalizations, emergency room visits, transfusion support, intravenous antibiotic use, and growth factor support.
18. Laboratory assessments for safety follow-up 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. Additionally, all treatment-related SAEs will be followed until resolution or stabilization. For subjects that had extramedullary disease at baseline, a CT scan is also required at this visit.

19. The investigators should ask for signs and symptoms of ventricular dysfunction as part of the routine AE monitoring for each cycle.
20. Information on survival and new anticancer therapy after last dose of study drug will be collected via telephone call every 12 weeks (± 14 days). Follow-up will continue to occur even though a subject may have started a new anticancer therapy after the last dose of study drug.
21. All drug supplies and associated documentation will be periodically reviewed and verified by the Study Monitor over the course of the study. A patient diary will be provided to each subject to record the study drug dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the study personnel for review, and will be reviewed by the Study Coordinator on a regular basis.

7.2 Subject Demographics/Other Baseline Characteristics

Refer to Table 3 for all windows for assessments.

7.2.1 Demography

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

7.2.2 Medical History

Clinically significant medical history findings (i.e., previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing of the informed consent, and considered relevant for the subject's study eligibility will be collected and captured, including baseline severity if ongoing, in the eCRF. "Clinically significant" is defined as any events, diagnoses or laboratory values requiring treatment, follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities. All conditions ongoing at the time of first study drug dose and all relevant conditions that may have resolved prior to the first dose of study drug should be recorded.

7.2.3 Other Baseline Characteristics

Other background information including history of disease, including the date of initial diagnosis and current disease status, staging at diagnosis and time of entry on this study, sites of disease, prior anticancer therapies, dates administered, responses and duration of response to these treatments will also be recorded. Prior medications/significant non-drug therapies will also be collected.

Not all patients with a diagnosis of WM need immediate therapy. Criteria for the initiation of therapy (Seventh IWWM) 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. Indications for Initiation of Therapy in Patients with WM[a]

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

[a] Dimopoulos et al, 2014, Seventh IWWM

Information will also be collected regarding childbearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, complete blood count [CBC] and blood chemistry, urinalysis, pregnancy test, ECG, and ECHO/MUGA). For further details on eligibility assessments, please see Table 3.

7.3 Efficacy

Response will be evaluated using an adaptation of the consensus panel criteria updated at the Sixth International Workshop (Owen et al 2013, NCCN Guidance Insights, 2012). Response will be assessed both with and without considering extramedullary disease (ie, IWWM-6 Including Extramedullary Disease and IWWM-6 "IgM-based"). Please refer to Appendix 2 for categorical response definitions and guidelines for special clinical and laboratory circumstances including response assessment in the case of dose hold or missing CT scans. Response categories include CR, VGPR, PR, Minor Response, SD, and PD. Additionally an IgM flare can be assigned during periods of study drug withholding (see Appendix 2 and guidelines for specific clinical or laboratory circumstances #5).

Response assessments will be performed, for both every 4 weeks (every cycle) starting from C2D1 for the first 48 weeks (12 cycles) then every 12 weeks (every 3 cycles) thereafter as indicated in Table 3, based on physical examination (in cases in which organomegaly is present), laboratory evaluations, quantitative serum immunoglobulins and serum immunoelectrophoresis with M-protein quantitation by densitometry (SPEP), radiologic assessment and bone marrow studies. All response assessments should be performed at the required visits as described above and should be entered into the eCRF. The data can be entered retrospectively in the eCRF according to the most recent version of the protocol.

Radiological assessment for extramedullary disease for those who have findings at baseline, by either IRC or investigator, will occur every 12 weeks for the first 48 weeks and then every 24 weeks thereafter until CT scan has normalized. Additionally, for subjects who had extramedullary disease at baseline, a CT scan is also required at the safety follow-up visit. For response assessments that occur during cycles where a CT scan is not required then results from prior scans (as long as within 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.

Change in serum IgM level from baseline will be based upon the IgM value from the central quantitative serum immunoglobulin assay, unless for assay limitations this is not possible, in which case the central M-protein level by densitometry (SPEP) will be used.

The serum IgM value (quantitative serum immunoglobulin/SPEP methodology) at C1D1 will serve as the baseline (last value prior to drug administration) for all assessments throughout the study except for patients who have undergone plasmapheresis. For patients who have undergone plasmapheresis, the pre-plasmapheresis serum IgM value (if available at screening) should be used. In the case of multiple prior consecutive plasmapheresis procedures during screening, the highest predose value (least confounded by plasmapheresis) should be used as the baseline.

For patients with cryoglobulinemia, blood samples (cryoglobulins/serum IgM/SPEP/serum immunofixation) should be collected and processed under warm conditions for baseline assessment and throughout the study.

Response assessments should be performed using results based on the same methodology in the same laboratory i.e., central or local throughout the study. Of note, all local labs, e.g. local serum IgM/SPEP or serum immunofixation or cryoglobulin results should be reported in the eCRF.

Per IWWM criteria, PD by increase in IgM requires a confirmatory blood draw which should be obtained at next scheduled IgM draw, or at a minimum of 4 weeks from the previous draw. In addition, PD requires a total increase of IgM of at least 500 mg/dL from lowest nadir. Subjects should remain on study drug until the central laboratory IgM testing confirms PD. Transformation of WM to large cell lymphoma (Richter's transformation) is considered as progressive disease and should not be recorded in the eCRF as an adverse event.

For patients with new disease symptoms, every effort should be made to obtain and document objective evidence of disease progression according to the disease-specific response criteria Appendix 2. Of note, progressive disease cannot be determined solely by the presence of B symptoms. Disease progression due to new symptomatic disease must be accompanied by objective evidence (e.g., imaging, laboratory value, biopsy, or bone marrow histology) consistent with the disease and associated response criteria for progression. For example, in the absence of IgM increase or other objective measures of disease progression, new B symptoms alone should not be the sole reason to discontinue a patient from study treatment.

If there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" response of PD (e.g. an increase in serum IgM level of at least 25% and 500 mg/dL from lowest nadir) after the study drug has been held for at least 7 consecutive days, an assessment response of IgM flare will be assigned instead of PD. The period to which 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., there is a drop in serum IgM level to below 25% and 500 mg/dL from lowest nadir) or the subject has a confirmed response of PD whichever comes first. During and following periods of study drug withholding, response assessments that would otherwise qualify as PD will initially be recorded as IgM Flare and NOT be considered as progressive disease. See Appendix 2 for all conditions and timing that must be met when assigning response for IgM Flare. Subjects may undergo plasmapheresis, when clinically indicated, during the first two cycles of study treatment. IgM response and nadir determination should be at least 4 weeks following the last plasmapheresis procedure. Subjects requiring plasmapheresis after Cycle 2 will be adjudged to have progressive disease.

At Screening, a bone marrow biopsy/aspirate, and CT scanning of the neck, chest, abdomen, and pelvis (including oral and/or intravenous contrast) will be conducted. If a bone marrow biopsy was performed within 42 days prior to randomization, the specimen will be sent for [redacted] analysis as described in Section 7.7. If a bone marrow biopsy is collected within 42 days of randomization, a fresh bone marrow aspirate must still be collected during the Screening period for flow cytometry and *MYD88* and *CXCR4* mutational analyses. With Medical Monitor (or designee) approval, archival tissue from a prior bone marrow biopsy may be sent to the central lab for assessment of mutation status; this will be allowed only if the fresh bone marrow biopsy/aspirate result in an indeterminate mutation result by the central lab. Quantitative serum immunoglobulins (IgM, IgG, IgA), serum immunoelectrophoresis with quantification of M-protein by densitometry and serum immunofixation, and β2-microglobulin will be drawn at Screening and followed as primary endpoints through the study. Complete blood count (CBC) will be drawn at Screening and followed every cycle. Cold agglutinins, cryoglobulins, anti-MAG (myelin associated glycoprotein), and serum viscosity will be drawn at Screening and followed if positive as markers of associated symptoms.

[redacted]

Bone marrow aspirate and biopsy will be obtained at Screening as described above and at 48 weeks (C13D1). Bone marrow aspirate and biopsy will also be repeated to confirm a CR if the subject has absence of M-protein and normal serum IgM level during the course of study treatment.

For subjects with evidence of extramedullary disease (lymphadenopathy and/or splenomegaly) by CT scan at Screening/baseline, the CT scan will be repeated every 12 weeks during the first 48 weeks beginning on C4D1 and every 24 weeks thereafter until PD or resolution of extramedullary disease, as well as at the safety follow-up visit. Please refer to Section 7.3.2.

Quantitative serum immunoglobulins (IgM, IgG, IgA) and serum immunoelectrophoresis with quantification of M-protein by densitometry and serum immunofixation will be performed on Day1 of every cycle for first 48 weeks with the Cycle 1 Day1 sample drawn at pre-dose, then every 3 cycles and thereafter. Please refer to Section 7.5.3 and Section 7.5.4.

In the event that 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 48 weeks (12 cycles), 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.

7.3.1 Physical Examination

Enlargement of lymph nodes and spleen is included in the physical examination at each visit for efficacy. Body systems (e.g. cardiovascular, respiratory etc.) should be evaluated at each visit when a physical examination is performed and any abnormalities recorded. See Section 7.4.2 for details of physical examination.

7.3.2 Radiological Tumor Assessment

Baseline radiological tumor assessment should be performed within 35 days of the randomization.

All subjects must have baseline CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites. An MRI of the head is required if clinically indicated. The CT portion of a PET/CT scan can also be performed as long as the same modality is used throughout the study.

For subjects with evidence of extramedullary disease (lymphadenopathy [note lymph nodes must measure >15mm in longest diameter (LDi)] and/or splenomegaly [measured craniocaudally > 130mm]) by CT scan at baseline, the CT scan will be repeated every 12 weeks during the first 48 weeks beginning on C4D1 and every 24 weeks thereafter until documented PD or complete resolution of extramedullary disease during the Treatment Phase by investigator according to consensus panel criteria updated at the Sixth International Workshop (Owen et al 2013 and Appendix 2; NCCN Guidance Insights, 2012). CT scans for post treatment efficacy follow-up will be performed for subjects discontinued due to the reasons other than PD at the follow-up visit. A

CT scan will also be repeated to confirm a CR if the subject has absence of serum monoclonal IgM protein and normal serum IgM level and had extramedullary disease at baseline and at the discretion of the investigator. At least one post-baseline CT scan is also required in situations where the baseline extramedullary disease assessment was determined to be absent by investigator and present by the IRC. The first follow-up CT scan for such patient should be performed within 30 days upon notification, ie, by the next clinic visit regardless of the protocol defined CT scan schedule and/or achievement of CR. Afterwards, follow-up CT scans should be obtained per the protocol schedule (with a minimum of 12 weeks between scans, at investigator's discretion).

All lesions found by imaging will be recorded at baseline as target (up to 10 lesions in extramedullary CRF) or non-target. Measureable lesions will be recorded in the eCRF at each imaging timepoint in 2 perpendicular dimensions: LDi and short diameter (SDi). SDi is defined as the longest diameter perpendicular to LDi.

Target lesions may become "too small to measure" (TSTM). While on study, all lesions (nodal and extranodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well).

An MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. The CT portion of a PET/CT scan can also be used. In Germany, an MRI may be used in place of CT in all subjects. However, in all cases the same modality should be used throughout the study. 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 reviewed by a central imaging vendor identified to this trial. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (e.g., central imaging vendor).

7.3.3 Bone Marrow Assessment

A unilateral bone marrow biopsy at Screening (within 42 days of the randomization, as long as no intervening therapy is administered) and a fresh bone marrow aspirate taken during Screening, followed by aspirate and biopsy at 48 weeks, at time of suspected CR, and as clinically indicated will be used to assess for bone marrow involvement by WM. Bone marrow for post treatment efficacy follow-up will be performed as per investigator's discretion for subjects discontinued due to the reasons other than PD.

All pathology samples will undergo central pathology review.

An aliquot of bone marrow specimen from Screening will be used for the mutation analysis, including but not limited to *MYD88* and *CXCR4* gene sequencing.

Optional bone marrow aspiration will be collected in subjects with progressive disease for studying the resistance mechanism.

7.3.4 Biopsy for Amyloidosis

For subjects with a known history of amyloidosis (based on screening bone marrow studies and indication of treatment initiation [Table 4]), fat pad biopsy or biopsy of other relevant tissue (e.g., bone marrow) will be collected at the time of suspected CR by IgM response.

7.3.5 Biopsy for Suspected Disease Transformation

Biopsy confirmation is necessary for subjects suspected to have disease transformation.

7.4 Safety

Safety assessments should be performed at all site visits throughout the study. Please see Table 3 for the schedule of the assessments and windows for assessments.

7.4.1 Adverse Events

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported. All AEs and SAEs, regardless of the relationship to the study drug, will be collected from the time of first dose of study drug. Secondary malignancies will be recorded as AEs and should be reported to the sponsor. Transformation of WM to large cell lymphoma (Richter's transformation) is considered as progressive disease and should not be recorded in the eCRF as an adverse event.

All subjects will be followed for safety 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 9.1. Important additional requirement for reporting SAEs are explained in Section 9.2.

In addition, arrhythmia signs/symptoms will be reviewed at every cycle. This will involve the investigators asking subjects for signs and symptoms of ventricular dysfunction via a brief questionnaire, as part of the routine AE monitoring for each cycle.

7.4.2 Physical Examination, Vital Signs, Height, Weight, Assessment of B symptoms, Re-evaluation of Baseline Reason(s) for Initiation of Therapy, and Review for Arrhythmia Signs/Symptoms

Physical examination, vital signs (sitting blood pressure, pulse rate, and body temperature), weight, B symptoms examination will be performed at the timepoints specified (See Table 3). Additionally, a brief questionnaire to review signs and symptoms of ventricular arrhythmia (e.g., shortness of breath, dizziness, or fainting) will be completed by all patients for both cohorts and the data will be recorded in the eCRF. These signs and symptoms will be monitored throughout the study at every visit. Height (cm) is determined at Screening only. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (≥ 38°C), and/or drenching night sweats.

Body systems (e.g. cardiovascular, respiratory etc.) should be evaluated at each visit when a physical examination is performed and any abnormalities recorded. A complete physical exam includes assessments of cardiovascular, respiratory, and neurological systems as well as the examination of the abdomen, lymph nodes, spleen, skin, oropharynx and extremities. As part of the tumor assessment, physical examination should also include the evaluation of the presence and degree of enlarged lymph nodes and splenomegaly. For a lymph node to be considered enlarged, the longest diameter should measure > 1.5 cm. Spleen should be measured craniocaudal.

In addition, baseline reason(s) for treatment initiation must be reviewed and documented at each visit (Day 1 of each cycle during the first 48 weeks [until C13D1), then every 3 cycles (every 12 weeks), and at EOT and Safety Follow-up Visits). Symptoms that triggered treatment will be followed until resolution(s) through the end of treatment.

7.4.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, each visit during study treatment, the End of Treatment Visit, and the Safety Follow-up Visit. Appendix 5 will be used to assess performance status.

7.4.4 Electrocardiogram

A 12-lead ECG will be performed locally in triplicate at Screening for all subjects. Subjects should be in the semi-recumbent or supine position.

For subjects assigned to the zanubrutinib arm, a 12-lead ECG in triplicate will be performed at pre-dose (within 30 min prior to dose) and at 2 hours (± 30 min) post-dose on C1D1 and C2D1, and one 12-lead ECG in triplicate performed at every 4 cycles thereafter (at C6D1, C10D1, etc.) until EOT. Where not specified, triplicate ECGs can be performed at either pre-dose or post-dose.

For subjects assigned to the ibrutinib arm, a 12-lead ECG in triplicate will be performed at C1D1, C2D1, and every 4 cycles thereafter (at C6D1, C10D1, etc) until EOT. The triplicate ECGs can be performed at either pre-dose or post-dose.

7.4.5 ECHO/MUGA

An ECHO/MUGA will be performed at the local lab at Screening, and when clinically indicated.

7.4.6 Quality of Life Assessment and Medical Resource Utilization

Subject in Cohort 1 (*MYD88*^{MUT}) must have quality of life assessed by EORTC QLQ-C30 and EQ-5D. Assessments will occur on Cycle 1 Day 1 (pre-dose) and every 12 weeks during the first 48 weeks, and then every 24 weeks thereafter. In addition, in Cohort 1, medical resource utilization, including the number of hospitalizations, length of hospital stay, and supportive care (e.g., transfusions, growth factor support, intravenous antibiotics) will be evaluated every cycle, including at Screening and Cycle 1 Day 1.

7.5 Laboratory Evaluations

Samples for CBC, Chemistry, and coagulation profiles will be drawn and analyzed locally. All other required blood samples (See Table 3) will be sent to central laboratory for analysis throughout the study. Windows for assessments are outlined in Table 3.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the Study Procedure Manual or in the Central Laboratory Manual.

Clinical chemistry, CBC, 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 necessary. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and urine tests performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

7.5.1 Hematology Studies

CBC with differential is required to be performed every cycle during the Treatment Phase. CBC include 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 (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 until toxicity resolves to ≤ Grade 2 or baseline (ANC ≥ 750/mm^3).

7.5.2 Clinical Chemistry

Clinical chemistry includes albumin, alkaline phosphatase, AST, ALT, bicarbonate, blood urea nitrogen (BUN) or urea, calcium, chloride, creatinine, 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 until toxicity resolves to ≤ Grade 2.

7.5.3 Quantitative Serum Immunoglobulins and β2-microglobulin

Quantitative serum immunoglobulins (IgG, IgM, IgA) and β2-microglobulin will be measured at the Screening Visit, on Day 1 of every cycle for the first 48 weeks with Cycle 1 Day 1 sample drawn at pre-dose, then every 3 cycles during the Treatment Phase. If subjects discontinue study drug due to reasons other than PD, serum immunoglobulin (i.e., IgG, IgM, IgA) will continue to be followed every 12 weeks. If serum immunoglobulin and β2-microglobulin performed at the screening are performed within 14 days of the first administration of study drug, they do not need to be repeated on Cycle 1 Day 1. It is recommended that sequential response assessments for individual subjects are performed in the same laboratory using the same methodology.

7.5.4 Serum Immunoelectrophoresis with M-Protein Quantitation by Densitometry (SPEP) and Serum Immunofixation

Serum immunoelectrophoresis with M-protein quantitation by densitometry (SPEP) and serum immunofixation will be performed at Screening, on Day 1 of every cycle for the first 48 weeks with Cycle 1 Day 1 sample drawn at pre-dose, then every 3 cycles during the Treatment Phase. If subjects discontinue study drug due to reasons other than PD, serum immunoelectrophoresis will continue to be followed every 12 weeks. If serum immunoelectrophoresis at the Screening is performed within 14 days of the first administration of study drug, it does not need to be repeated on Cycle 1 Day 1. Additionally, see note below in Section 7.5.5 regarding retesting serum immunoglobulins in subjects with cryoglobulinemia.

7.5.5 Cold Agglutinins, Cryoglobulin, Anti-MAG, Serum Viscosity

Cold agglutinins, cryoglobulin, anti-MAG (myelin associated glycoprotein), serum viscosity blood tests will be performed at Screening. If there are abnormal findings for any of these laboratory assessments at Screening, follow-up is required every cycle for the first 48 weeks, then every 3 cycles starting C13D1 and at time of suspected CR.

Subjects who have cryoglobulinemia at Screening and are confirmed by the central test, should be tested for the presence of cryoglobulins **at the local laboratory** prior to C1D1. The C1D1 sample will serve as the baseline. Repeat testing is required at every visit at the local laboratory or central laboratory until cryoglobulin testing has normalized (negative result), and then be assessed every 3 cycles and at time of suspected CR. When samples are collected and tested at local laboratories, the local results should be recorded in the eCRF. In addition, the serum immunoglobulins/SPEP and

serum immunofixation assays should also be retested prior to C1D1, using the residual cryoglobulin blood sample if available, at the local laboratory, which should be collected and processed similarly to the cryoglobulins under warm conditions. Only when serum immunoglobulins cannot be quantified, the serum immunoelectrophoresis sample will need to be re-collected, processed, and analyzed at the local laboratory under warm conditions. If neither the local laboratory baseline serum IgM nor SPEP M-protein was available, then the central laboratory serum IgM should be collected in addition and may be used for response assessment throughout the study. If central serum IgM has shown to be reliable despite the cryoglobinemia, the local laboratory serum IgM may no longer be required.

The samples (cryoglobulin and serum immunoglobulins) should always be collected and processed under warm conditions at the local or central laboratory throughout the study to ensure that the same methodology is used throughout the study. The results of all local testing should be entered into the EDC once they are available. If it is not possible to perform the cryoglobulin or serum immunoglobulin testing at the local laboratory, the Clinical Research Associate or BeiGene should be contacted as soon as possible.

7.5.6 Iron, Total Iron Binding Capacity (TIBC), and Ferritin Tests

Iron, TIBC and ferritin tests will be performed at Screening only. If abnormal, iron supplementation should be provided per investigator's discretion prior to initiation of study treatment.

7.5.7 Coagulation

The coagulation profile includes prothrombin time (PT), which will also be reported as international normalized ratio (INR). The coagulation profile will be performed at Screening only.

7.5.8 Urinalysis with Dipstick

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal (may be at investigator discretion except when urine protein ≥ 2+). Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated. All these tests will be performed in local laboratory.

7.5.9 Pregnancy Test

A serum pregnancy test will be performed at Screening within 7 days of randomization and end of treatment in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Cycle 1 Day 1, and then on Day 28 of every cycle (which can be performed on Day 1 of the following cycle). Pregnancy tests must be continued every 4 weeks (cycle) for at least 90 days after the last dose of study drug. At the last dose of study drug, a serum pregnancy test is required (for practicality, it will be performed at End of Treatment Visit). 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.

7.5.10 HIV and Hepatitis B/C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at Screening. The hepatitis B testing includes hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis B surface antigen (HBsAg) as well as hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes Hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible. Subjects HBsAg negative, HBcAb positive and HBV DNA negative must undergo monthly HBV DNA Screening PCR. If, during monthly monitoring of HBV DNA by PCR, the value is between 20 IU/mL and 100 IU/mL then the HBV DNA level should be rechecked within 2 weeks. Study drug should be held and anti-viral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher then study drug should be stopped and anti-viral therapy initiated. Subjects positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA Screening. Subjects with known HIV are excluded from the study. Subjects with detected HCV RNA should stop study drug and anti-viral therapy should be initiated. The Medical Monitor or designee should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 5 below, shows how the results for HBV, and HBV 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])

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA "Not detected"*[1] *Perform monthly monitoring of HBV DNA*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*[1]
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not detected"* [1] *Perform monthly monitoring of HCV RNA*	**Antibody (+)** *HCV RNA Detected*[1]

DNA: deoxyribonucleic acid; HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; RNA: ribonucleic acid

1. Please refer to Section 7.5.10 above.

7.6 Pharmacokinetics

Blood will be collected to characterize the PK of zanubrutinib and/or its major metabolites from all subjects on Arms A and C. Close monitoring of zanubrutinib drug concentrations may be needed by taking additional unscheduled PK samples in the event of suspected drug-drug interactions (eg, when a strong or moderate CYP3A inducer must be used for control of infection).

7.6.1 Pharmacokinetic Blood Samples

Pharmacokinetic samples will be collected from subjects randomized to Arms A and C (zanubrutinib) only at the following time points: pre-dose (within 30 min prior to dose), 2 hours (± 30 min) post-dose and before subject discharge (3-6 h post-dose) on Cycle 1 Day 1 and Cycle 2 Day 1. The time of study drug administration on the day prior to Cycle 2 Day 1 must be recorded on the eCRF.

Blood samples (2 mL) for PK analysis will be collected via the intravenous cannula pre-dose and at the time points specified in Table 3. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Study Manual.

Samples will be shipped to the central laboratory where they will be stored and batch shipped to designated bioanalytical lab for quantification of plasma zanubrutinib concentrations using a validated method.

7.6.2 Effects of Plasmapheresis on PK of Zanubrutinib

For subjects receiving plasmapheresis (in Cycle 1 or Cycle 2 or beyond), below are additional procedures to follow:

- Subjects are recommended to come in the clinic to receive zanubrutinib dosing on the day of plasmapheresis. To properly assess the impact of plasmapheresis on zanubrutinib PK, plasmapheresis session is to commence between 2 to 3 hours (T_{max}) following zanubrutinib dosing.
- Zanubrutinib dosing time and the start and end time of each plasmapheresis session must be recorded in the database.
- For subjects receiving plasmapheresis, additional PK samples (in addition to those noted in Section 7.6.1) will be collected at the following time points: immediately before the start of plasmapheresis, approximately an hour after the start of the procedure, and 30 min after the end of the procedure. PK collection time will be recorded in the database.
- For each plasmapheresis session, the volume of removed plasma will be measured and recorded in eCRF and an aliquot will be stored at a temperature of -20ºC or lower until analysis.
- Zanubrutinib concentrations in both circulating and removed plasma will be measured using a validated method.

[redacted]

Additionally, the Sponsor would like to retain/archive/save any residual or extra samples that are not analyzed in Study BGB-3111-302 for additional exploratory [redacted] studies and analyses that may be conducted at a later time. The samples will be used only for studies related to WM.

The biological samples will be labeled with a unique code and be stored under BeiGene's control for up to 20 years, at which point they will be destroyed. During and after the study, the subject has the right to have any remaining sample material destroyed by the Sponsor or returned to the subject's Study Doctor at any time. Any [redacted] generated from the additional research during the study or after the study is completed will belong to the Sponsor and will not become part of the patient's medical record.

Disclosure of any data obtained from the optional studies will be restricted. Site monitors, auditors, ethics committees and/or regulatory authorities may also access the patient data in connection with such additional research. Patient data will be retained as long as it is useful for such purposes. If the results of such studies are published or presented in a meeting, the patient's identity will not be disclosed.

7.8 Appropriateness of Measurements

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

[redacted]

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 eCRFs 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 of the protocol-required information to be reported to the sponsor on each study subject.

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

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

8.2 Data Management/Coding

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

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

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

8.3 Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also

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

9 SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring 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. 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. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

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 medicinal product, whether or not considered related to the medicinal product.

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

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

Examples of an AE include:

- Worsening of 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.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by

the sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.1.1.1 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03.

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.

9.1.1.2 Assessment of Causality

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

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

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (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 or other concomitant AEs).

9.1.1.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each 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, the subject is lost to follow-up, or the subject withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a 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 form, with all changes signed and dated by the investigator. The updated SAE report form should be resent to the sponsor within the time frames outlined in Section 9.2.2.1 and the eCRF should be updated accordingly.

9.1.2 Laboratory Test Abnormalities

Abnormal laboratory findings (e.g., clinical chemistry, CBC, coagulation, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, etc.) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 9.1.1) or an SAE (as defined in Section 9.2). The definition of clinically significant abnormal laboratory findings is left to the judgment of the investigator. In general, these are the laboratory test abnormalities that are associated with clinical signs or symptoms, require medical intervention, lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or require further diagnostic investigation. 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.

- Results in disability/incapacity.

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

- Is a congenital anomaly/birth defect.
- Is considered a significant medical AE by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered SAEs:

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

9.2.2 Reporting

9.2.2.1 Timeframes for Submitting Serious Adverse Events

Serious adverse events must be reported within 24 hours of investigator's first knowledge to the sponsor as described in Table 6 once the investigator determines that the event meets the protocol definition of a SAE.

Table 6. Timeframe for Reporting Serious Adverse Events to the Sponsor

Type	Timeframe for Initial SAE Report	Documentation Method	Timeframe for Follow-up SAE Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report form	As expeditiously as possible	Updated SAE report form	Email or fax SAE report form*

SAE: Serious Adverse Event;

*The SAE must also be reported in the EDC System by completing the electronic Case Report Form.

9.2.2.2 Completion and Transmission of the Serious Adverse Event Report Form

Once an investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.2.2.1. The SAE report form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the sponsor or designee within the designated timeframes.

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

The investigator will always provide an assessment of causality for each SAE as described in Section 9.1.1.2.

The sponsor will provide contact information for the SAE report form receipt. The SAE must also be reported in the EDC System by completing the electronic Case Report Form.

9.2.2.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.2.2.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

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

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

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

9.2.2.5 Specific Instructions for Recording Adverse Events and Serious Adverse Events

Disease Progression

Disease progression (including fatal disease progression) is expected in this study population, and is measured as an efficacy endpoint, therefore should not be reported as an AE term. Instead, the signs, symptoms or clinical sequelae that result from 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 experienced multi-organ 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 an SAE. 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 the study drug.

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

Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death should be reported as an event, e.g., "Death", "Death of unknown cause", or "Death unexplained."

9.2.2.6 Serious Adverse Event Related to Study Participation

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

9.2.2.7 Expedited Reporting to Health Authorities, Investigator, Institutional Review Boards and Ethics Committees

The sponsor will promptly assess all SAE against cumulative study drug experience to identify and expeditiously communicate new safety findings to health authorities, investigators, institutional review boards and ethics committees based on applicable legislation.

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

- Zanubrutinib (BGB-3111) Investigator's Brochure
- Local prescribing information for ibrutinib

9.3 Pregnancies

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. All post--study assessments will be collected at the time of discontinuation as described in Table 3.

If a female subject or the partner of a male subject becomes pregnant while participating in this study, a pregnancy report form is required to be completed. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the sponsor within 2

weeks of learning of a subject's or male subject's female partner's pregnancy. The subject or male subject's female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. 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 9.1.1.3.

An abortion, whether accidental, therapeutic or spontaneous, should always be reported as an SAE as described in Section 9.2.2.1. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study drug by the investigator, will be reported to the sponsor as described in Section 9.2.2.2. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as an SAE.

9.4 Lack of Efficacy

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

9.5 Data Monitoring Committee

An independent DMC will monitor safety data periodically throughout the study. An efficacy and safety interim analysis, which occurs approximately 6 months after the first 50 relapsed/refractory subjects randomized from Cohort 1, will be implemented in the study. A stop in recruitment is not planned for this interim safety review. At regular safety reviews, data review will include but not be limited to deaths, SAEs, adverse events leading to dose reduction, dose interruption, or drug discontinuation. The DMC may recommend study modification, including termination of the study due to efficacy and/or safety concerns. Subsequent safety data review is outlined in DMC charter.

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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.

Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

10.1 Primary, Secondary and Exploratory Study Endpoints

Please refer to Section 3 for a full listing of study endpoints.

10.2 Statistical Analysis

All inferential statistics described in this Section refer to the efficacy comparisons of Arms A and B in Cohort 1 which are the primary/secondary objectives of the study. Separate descriptive statistics in Cohort 2 will be used to report the efficacy of zanubrutinib in Arm C.

10.2.1 Analysis Sets

The Intent to Treat analysis set (ITT) includes all enrolled subjects who are assigned to a treatment arm. The Relapsed/Refractory analysis set in Cohort 1 will be the primary analysis set used for efficacy analyses.

The Relapsed/Refractory analysis set (a subset of the ITT analysis set) includes all randomized subjects with at least 1 prior line of therapy as determined by the IRT system.

The Safety analysis set includes all subjects who received any dose of zanubrutinib or ibrutinib. Subjects will be assigned to the treatment arms as treated. The Safety analysis set will be used for all safety analyses.

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

The PK analysis set includes all subjects who have at least one post-dose zanubrutinib concentration.

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 by treatment arm. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF. The end of study status

(alive, dead, 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 by treatment arm in ITT and Safety analysis sets using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial WM diagnosis; categorical variables include sex, age group (< 65 vs. ≥ 65 years), race, disease stage, ECOG-PS, prior line of therapy for WM (0 vs. 1-3 vs. >3 prior therapies), geographic region, *MYD88/CXCR4* gene mutation status, presence of extramedullary disease (yes vs. no), baseline bone marrow involvement (< 50% vs. ≥ 50%), WM IPSS (low, intermediate, high), and β2 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 World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the 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

Comparison of the primary endpoint CR/VGPR rate in Cohort 1 assessed by independent review committee will be tested using hierarchical fixed-sequence procedure under the null and alternative hypotheses as follows:

H_0: $RR_A = RR_B$

Ha: $RR_A > RR_B$

where RR_A is the CR/VGPR rate in Arm A (zanubrutinib) and RR_B is the CR/VGPR rate in Arm B (ibrutinib).

Testing for above hypotheses will be performed in the Relapsed/Refractory analysis set first at 1-sided alpha of 0.025. If the result is in the Relapsed/Refractory analysis set is statistically significant, the primary objective has been met and further testing will be performed in the ITT analysis set at 1-sided alpha of 0.025.

A Cochran-Mantel-Haenszel (CMH) test of rate difference based on *CXCR4* status (WHIM vs WT/missing) and prior line of therapy (1-3 vs. >3 for Relapsed/Refractory analysis set analysis and 0 vs 1-2 vs >3 in ITT analysis) will be performed for hypothesis testing at the 0.025 level (1-sided) in the corresponding analysis set of Cohort 1.

A CMH 95% stratified confidence interval (CI) of rate difference (RR_A-RR_B) with each rate weighted by number of subjects in each stratification factor combination will be constructed for the Relapsed/Refractory analysis set and the ITT analysis set, respectively. A Clopper-Pearson 95% CI of CR/VGPR rate within each arm will be constructed for the Relapsed/Refractory analysis set and the ITT analysis set, respectively.

The primary efficacy analysis in Cohort 1 will be conducted approximately 12 months after the cohort assignment of the last subject.

Sensitivity analysis of the primary endpoint will be performed using investigator assessment. An unstratified analysis using exact method will also be performed in the sensitivity analysis.

10.2.5.2 Secondary Efficacy Analysis

If the primary efficacy analysis is statistically significant in Cohort 1, secondary endpoints will be tested in the analysis set where the null hypothesis for primary efficacy endpoint is rejected.

MRR

MRR will be tested for non-inferiority of Arm A vs Arm B. The null and alternative hypotheses of MRR are set as follows:

H_0: MRR_A-$MRR_B \leqslant$-8%

Ha: MRR_A- MRR_B>-8%

where MRR_A is the major response rate in Arm A (zanubrutinib) and MRR_B is the major response rate in Arm B (ibrutinib) based on respective analysis sets.

MRR will be compared between Arms A and B. It will be analyzed using the same methods as described in the primary endpoint. A Cochran-Mantel-Haenszel (CMH) test of rate difference adjusting for stratification factors (CXCR4 status [WHIM vs WT/missing] and prior line of therapy [1-3 vs >3 for Relapsed/Refractory analysis set analysis and 0 vs 1-2 vs >3 in ITT analysis set analysis]) will be performed at the 0.025 level (1-sided). Equivalently, the 2-sided 95% CI for the weighted rate difference (weighted by the number of subjects in each stratification factor combination) will be constructed to examine whether it excludes -8%. Furthermore, superiority can be claimed if the lower limit excludes 0.

Justification of non-inferiority margin

The same non-inferiority margin will be used for both ITT and Relapsed/Refractory analysis sets.

Since no randomized trial has been conducted in WM, the ibrutinib treatment benefit over placebo can only be estimated from the single-arm ibrutinib Phase 2 trial in which the MRR is 0.73 with 95% CI (0.60, 0.83). As a ≥ 50% reduction of IgM is impossible without treatment, MRR can be considered 0% in the placebo treated subject. Therefore, the lower bound of 95% CI (i.e., 60%) can be used as the treatment effect of ibrutinib over placebo (M1). A NI margin of 8% (M2) is proposed assuming 86.7% of the ibrutinib benefit over a placebo is retained. With close to 90% of the ibrutinib effect preserved, the 8% NI margin in MRR is clinically justified. The loss of the ibrutinib treatment benefit is well within the clinically acceptable range. It is worth noting that the NI of MRR will only be performed after the superiority of zanubrutinib over ibrutinib in CR/VGPR rate, which is closely correlated with MRR, has been demonstrated. Hence, a numerically higher MRR in zanubrutinib is certainly expected if the NI test of MRR is to be performed. The inclusion of the NI test of MRR is mainly based on the sample size consideration in a rare disease setting where statistical significance might not be shown in a superiority test with a clinically meaningful MRR difference (e.g., 12% higher MRR in zanubrutinib over ibrutinib) in 150 randomized relapsed/refractory subjects.

Best overall response (BOR) which is defined as the best response recorded from cohort assignment date until data cut or start of new antineoplastic treatment. Subjects with no post-baseline response assessment (regardless of reason) will be considered non-responders for best overall response. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, VGPF, PR, Minor Response, SD, and PD) will be presented.

Other secondary endpoint analyses:

Progression-free survival (PFS) will be analyzed at the time of the primary analysis of VGPR/CR rate. In addition, subjects will continue to be followed for PFS events after the primary analysis of VGPR/CR tate, until the final analysis of PFS. During this period, the sponsor will keep maintaining trial integrity according to the Data Integrity Protection Plan (DIPP). Timing of the final analysis of PFS will be specified in the statistical analysis plan.

Distribution of PFS will be estimated using the Kaplan-Meier (KM) method per treatment arm. PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

A stratified log-rank test with CXCR4 and prior line of therapy as strata (CXCR4 status [WHIM vs WT/missing] and prior line of therapy [1-3 vs. >3 for Relapsed/Refractory analysis set analysis and 0 vs 1-2 vs >3 in ITT analysis set analysis]) will be used to test the PFS differences between Arms A and B. The Cox regression will be used to estimate the hazard ratios (HR) of PFS_A vs PFS_B. A 95% CI of HR in PFS will be constructed.

Median PFS, if estimable, will be estimated using the KM method. Its 2-sided 95% CIs, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. KM estimates of PFS will be plotted over time. The PFS rate at selected timepoints such as, 12, 18 and 36 months, defined as the percentages of subjects in the analysis set who remain alive and progression-free at the specified time points, will be estimated using KM method along with the corresponding 95% CI constructed using Greenwood's formula.

For responders with PR or above, the duration of CR/VGPR/PR within subjects who have achieved major response will be analyzed similarly as PFS.

Indications for initiation of therapy (see Table 4) will be documented for all subjects at baseline visit. Symptoms that triggered treatment will be followed at during and end of treatment visits until resolution. Percentages of subjects with resolution of each and all baseline symptom(s) will be summarized; and compared between Arms A and B using Fisher's exact test.

Maximum decrease in percentage of lymphoplasmacytoid lymphocytes in bone marrow will be compared using analysis of variance model with treatment arm (A vs. B) as group variable. Percentage of subjects with decreased percentage of lymphoplasmacytoid lymphocytes after the start of study medication will also be compared using Fisher's exact test. Percentages of subjects with resolution and/or reduction of pretreatment lymphadenopathy and/or splenomegaly according to CT scan will be summarized separately; and compared using Fisher's exact test.

10.2.5.3 Exploratory Efficacy Analysis

[redacted]

[redacted]

10.2.6 Pharmacokinetic Analyses

PK analysis set will be carried out to include plasma concentrations from this trial in an existing model. PK parameters such as C_{min} will be summarized, and additional PK parameters such as apparent clearance of the drug from plasma (CL/F) and area under the plasma concentration-time curve ($AUC_{[0-24]}$) may be derived from the PK analysis set if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

The impact of plasmapheresis on zanubrutinib exposure will be estimated by comparing the AUC of zanubrutinib in subjects with or without the plasmapheresis procedure.

10.2.7 [redacted]

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. 2015a). All subjects will have sequencing of *MYD88* and *CXCR4* performed on bone marrow samples which will be sent to the central laboratory for analysis.

10.3 Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (CBC, clinical chemistry, coagulation, and urinalysis), vital, physical exams and ECGs findings will also be used in determining the safety. Descriptive statistics will be used to analyze all safety data by treatment arm, as well as by combining Arms A and C in the Safety analysis set.

[redacted]

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

10.3.3 Laboratory Analyses

Clinical laboratory (i.e., CBC, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter by treatment arm. 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 (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for

categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI-CTCAE v4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (e.g., 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, temperature, weight) and changes from baseline will be presented by visit and treatment arm for all visits. Vital signs will be listed by subject and visit.

10.3.5 Electrocardiogram

Descriptive statistics for baseline ECG parameters will be presented.

10.4 Sample Size Consideration

The sample size calculation is based on the comparison of the primary endpoint CR/VGPR rate in the Relapsed/Refractory analysis set in Cohort 1. Assuming RR_A=0.35 and RR_B=0.15, seventy-five subjects per arm (150 total) provide a power of 0.814 in testing RR_A versus RR_B in the Relapsed/Refractory analysis set in Cohort 1 using a normal approximation to binomial test with a two-sided significance of 0.05. Assuming MRR_A=0.90 and MRR_B=0.80, the power of demonstrating non-inferiority of zanubrutinib in the Relapsed/Refractory analysi set is 85.5% when a NI margin of 0.08 is used.

In addition to 150 replased/refractory subjects, approximately 20% (38) treatment-naïve subjects with $MYD88^{MUT}$ will be enrolled in Cohort 1.

Assuming $MYD88^{MUT}$ mutation is present in 90% of the enrolled subjects, a total of approximately 210 subjects will be enrolled in Cohort 1 and Cohort 2 combined.

10.5 Interim Analysis

An interim analysis, which occurs approximately 6 months after the first 50 relapsed/refractory subjects are randomized from Cohort 1, will be implemented in the study. This analysis is for futility only. No recruitment stop is planned for this interim analysis. If futility is demonstrated in the interim analysis, enrollment will be halted and safety and efficacy data will be further evaluated before making the decision of stopping the study permanently. Otherwise, the enrollment will be continued to 150 relapsed/ refractory subjects in Cohort 1. Details of the interim analysis will be provided in the SAP.

10.6 Other Statistical Issues

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 CR/VGPR rate, MRR and ORR. Non-responders of the response categories will be excluded in the corresponding analysis of duration of response. A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the SAP.

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

11 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

11.1 Regulatory Authority Approval

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

11.2 Investigator Responsibilities

11.2.1 Good Clinical Practice

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

Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify BeiGene or its authorized representative 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 by the principal investigator and the study center 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 (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. 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 or its authorized representative 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 (or sponsor, where applicable) 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 subject consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.2.3 Informed Consent

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

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

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patients' clinical record. Informed consent may be obtained before the 35-day Screening period. Consent must be obtained using the most current version of the form approved by the ethics committee.

Repeating Screening procedures or tests are allowed if the patient did not previously meet the inclusion and exclusion criteria or if needed to have a documented result within the protocol-specified Screening window. The maximum number of repeats for a failed screening test is one within the screening window, and a patient may be re-screened no more than once.

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

11.2.4 Investigator Reporting Requirements

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

11.2.5 Confidentiality

Information on maintaining subject confidentiality and privacy in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent form process, either as part of the informed consent form (ICF) or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials (if allowed), date of birth (as permitted by local law), and an identification code (i.e., 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.

The CRFs exist within an electronic data capture (EDC) system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and applications of electronic signatures before the study start and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing an electronic signature within the EDC system. After final database lock, the Investigator will receive a copy of the subject data from that site (e.g., paper, CD, or other appropriate media) for archiving the data at the study site.

11.2.7 Drug Accountability

The investigator or designee (i.e., 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, quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials (if allowed), the initials of the person dispensing the medication, and quantities destroyed or returned to BeiGene. 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. A patient diary will be provided to each subject to record the study drug dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the site personnel for review, and will be reviewed by the Study Coordinator on a regular basis.

11.2.8 Inspections

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

11.2.9 Protocol Adherence

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

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

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

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

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.

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

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

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.
- Shipment of PK samples to assay laboratories.

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 with this protocol, GCP, the clinical study agreement or applicable laws and regulations. If the sponsor determines such action is

needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action 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 provided to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

11.5 Records Retention and Study Files

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, Screening ECHO/MUGA, 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 (e.g., 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 or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all 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.

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.

11.6 Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a 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.

11.7 Joint Investigator/Sponsor Responsibilities

11.7.1 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.

11.7.2 Access to Information for Auditing or Inspections

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

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13 APPENDICES

Appendix 1: Signature of Investigator

PROTOCOL TITLE: A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)

PROTOCOL NO: BGB-3111-302

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

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: _____

_____

_____

_____

[redacted]

Appendix 2: WM Response Assessment

Categorical Response Definitions

IWWM-6 "IgM-based" without consideration of EMD[a] (Modified Owen 2013)

Response category	Definition
Complete response (CR)	Normal serum IgM values *Note: An IgM/ SPEP M protein level obtained within 4 weeks post-plasmapheresis cannot be used to determine a response of CR* • Disappearance of monoclonal protein by immunofixation *Note: If immunofixation status is not reported/not interpretable for any available timepoints, the best possible response is VGPR. One negative immunofixation is sufficient to be called CR for a particular visit. Once a negative immunofixation has been reported for a visit, any subsequent visits with immunofixation status not reported or not interpretable can be CR as long as all remaining data supports a continued CR status* Negative cryoglobulinemia if cryoglobulinemia was Positive at baseline. Otherwise, if cryoglobulinemia was negative or not available at baseline, a negative cryoglobulinemia assessment at post-baseline is not required for an overall timepoint assessment of CR.
Very good partial response (VGPR)	≥90% reduction in serum IgM level from baseline or normal serum IgM values
Partial response (PR)	≥50% reduction of serum IgM from baseline
Minor response (MR)	At least 25% but <50% reduction of serum IgM from baseline
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	Confirmed ≥25% increase in serum IgM and total increase of ≥500 mg/dL from nadir (on treatment)[b,c]

[a] IgM assessment should be made incorporating only IgM-related clinical data including IgM, M protein (SPEP/paraprotein), serum immunofixation, plasmapheresis, cryoglobulinemia and drug hold, as applicable. If the patient has developed new symptomatic disease attributable to WM, the overall response will be assessed as disease progression.

[b] 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

[c] If there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" response of PD (e.g. there is an increase in IgM level of at least 25% and 500 mg/dL from nadir) after the study drug has been held for at least 7 consecutive days, an assessment of IgM flare will be assigned instead of PD. The period to which 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 or the subject has a confirmed response of PD*, whichever comes first. Please see Guidelines for specific clinical or laboratory circumstances and timing below.

Categorical Response Definitions

IWWM-6 Including EMD (Modified Owen 2013)

Response category	Definition
Complete response (CR)	Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline)[a,d]
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline[a] or normal serum IgM values Improvement in extramedullary disease, lymphadenopathy/splenomegaly if present at baseline [a,d] No new signs or symptoms of active disease
Partial response (PR)	• ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline) [a,d]
Minor response (MR)	At least 25% but <50% reduction of serum IgM from baseline
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)[b,c] • New lymph nodes >1.5 cm, or ≥50% increase from nadir in sum product of diameter (SPD) of >1 node, or ≥50% increase in longest diameter of a previously identified node • New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

[a] 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

[b] 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

[c] If there is a rapid rise in serum IgM level or an increase in known extramedullary disease leading to an "apparent" response of PD (e.g. there is an increase in IgM level of at least 25% and 500 mg/dL from nadir) after the study drug has been held for at least 7 consecutive days, an assessment of IgM flare will be assigned instead of PD. The period to which 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 or the subject has a confirmed response of PD*, whichever comes first. Please see Guidelines for specific clinical or laboratory circumstances and timing below.

[d] If only physical exam (PE)is available and the clinical assessment is indicative of an unequivocal improvement from baseline (enlarged spleen have regressed, abnormal lymph nodes have reduction in measurements), then the reduction in extramedullary disease can be assessed by PE alone.

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 Screening and confirmed by the central test, the local laboratory will retest for the presence of cryoglobulins prior to C1D1. The C1D1 sample will serve as the baseline. In addition, serum quantitative immunoglobulins should be retested using the residual cryoglobulin blood sample at the local laboratory, which should be collected and processed under warm conditions. Only when serum immunoglobulin cannot be quantified, serum immunoelectrophoresis sample will need to be re-collected, processed, and analyzed at local laboratory under warm conditions. The blood samples (for cryoglobulin and serum immunoglobulins) should be collected and processed under warm conditions at the local laboratory throughout the study to ensure that the same methodology is used throughout the study. The results for cryoglobulin and serum immunoglobulins would need to be recorded in the eCRF at all required visits. It is recommended that the blood samples (cyroglobulins/serumIgM/SPEP/serum immunofixation) should be sent to central lab for analysis in addition to the local lab and collected and processed under warm conditions throughout the study.

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, or the highest predose value (least confounded by plasmapheresis) will serve as the baseline value for response assessment throughout the study. IgM response and nadir determination should be at least 4 weeks following the last plasmapheresis procedure). Subjects requiring plasmapheresis after Cycle 2 will be adjudged to have progressive disease.

5. Assigning IgM Flare due to study drug hold

An assessment of IgM flare will be assigned instead of PD after study drug has been held at least 7 consecutive days and there is a rapid rise in serum IgM level (or an increase in known extramedullary disease for resonse that includes extramedullary disease assessment) leading to an "apparent" response of 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. there is a drop in IgM level below 25% and 500 mg/dL from nadir) or the subject has a confirmed response of PD*, whichever comes first. When assigning response for IgM flare after drug is restarted, the following conditions must be met:

- If IgM levels and/or known extramedullary disease continues to decrease from peak IgM level (off study drug) or peak (highest SPD) in extramedullary disease, when drug was held, PD will not be recorded. If, however, while on study drug the IgM level or SPD increases above the peak level that occurred when drug was held, and IgM level or SPD increase is confirmed with a repeat assessment 4 weeks later, the subject will be considered to have PD and IgM will not be assessed.
- If, after 10 weeks of study drug re-initiation (to allow for fluctuation), the next assessed IgM level shows either a continued rise at each timepoint from the initiation of the drug hold or no decrease from the previous visit, then a serum IgM level obtained 4 weeks later must be used to confirm PD. PD will be confirmed if the subsequent IgM measurement is greater than or equal to the previous IgM assessment (first IgM assessment post 10 weeks study drug initiation). The response assessment of PD* will be recorded at the first visit 10 weeks after study drug re-initiation.
- Similarly, if apparent PD was due to an increase in extramedullary disease and after 10 weeks of study drug re-initiation the evaluation of extramedullary shows either a continued rise from the initiation of the drug hold or no decrease from the previous visit, then PD is confirmed and the response assessment of PD will be recorded at the first visit 10 weeks after study drug re-initiation.
- If during drug re-inititation the IgM level decreases and then rises at any timepoint thereafter:
    - If at the time of the IgM rise, the IgM level still qualifies as PD* then a confirmatory serum IgM level obtained 4 weeks later must be used to confirm PD*. PD will be confirmed if the subsequent IgM measurement is greater than or equal to the previous IgM assessment (IgM at the time of the initial IgM rise following IgM decrease). The response of PD will be recorded at the time of the initial IgM rise following the IgM decrease.
    - If at the time of the IgM rise, the IgM level does not qualify as PD* then continue response assessments as described above.

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 500 mg/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 3: CYP3A Inhibitors and Inducers

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

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers.
Abbreviation: CYP: cytochrome P450.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

Appendix 4: Sensitive CYP2C8, CYP2C19 Substrates or CYP2C8, and CYP2C19 Substrates with a Narrow Therapeutic Index

CYP2C8 Substrates	**CYP2C19 Substrates**
repaglinide[1]	**Anti-epileptics:**
paclitaxel	S-mephenytoin[1,2]
	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 (e.g., Torsades de Pointes).

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers.
Abbreviations: AUC: area under the plasma concentration time curve; CYP: cytochrome P450; NTI: narrow therapeutic index.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for drug interaction information or contact the medical monitor of the protocol.

Appendix 5: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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 6: List of Country Specific Amendments

Amendment 1.1-UK: **17 January 2017**

Amendment 1.3-Germany: **30 January 2017**

Amendment 1.4-Sweden: **24 February 2017**

Amendment 2.1-France: **02 November 2017**

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