CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma
Protocol Identifier:	BGB-3111-214
Phase:	2
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	Marginal zone lymphoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA
Reference Number:	EudraCT 2018-001284-24
IND Number:	125326
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol:	01 June 2018
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This protocol has been developed in collaboration with the Australasian Leukemia and Lymphoma Group.

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FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma

BeiGene, Ltd. Approval:

[redacted]

03 JUNE 2020

Date

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Zanubrutinib (BGB-3111)

Title of Study: A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma

Protocol Identifier: BGB-3111-214

Phase of Development: 2

Number of Patients: Approximately 65

Study Centers: Approximately 60

Study Objectives:

Primary:

- To evaluate the efficacy of zanubrutinib (also known as BGB-3111) in relapsed or refractory marginal zone lymphoma as measured by overall response rate in accordance with the Lugano Classification (Cheson et al 2014) (Appendix 2) determined by Independent Review Committee (IRC)

Secondary:

- To evaluate the efficacy of zanubrutinib in relapsed or refractory marginal zone lymphoma in accordance with the Lugano Classification (Cheson et al 2014) (Appendix 2) as measured by the following:
    - Overall response rate determined by investigator assessment
    - Progression-free survival determined by IRC and by investigator
    - Overall survival
    - Duration of response determined by IRC and by investigator
    - Time to response determined by IRC and by investigator
    - Time to treatment failure
    - Time to next line of therapy for marginal zone lymphoma
- To evaluate patient-reported outcomes
- To determine the safety of zanubrutinib
- To determine pharmacokinetic parameters of zanubrutinib

Exploratory:

- Overall response rate in accordance with Cheson et al 1999 as determined by the IRC

Study Design:

This is a Phase 2, open-label study of zanubrutinib in approximately 65 patients with relapsed or refractory marginal zone lymphoma (R/R MZL). The primary efficacy endpoint is overall response rate (ORR) (complete response [CR] + partial response [PR]) in accordance with the Lugano Classification (Cheson et al 2014) determined by IRC. Response in accordance with the Lugano Classification (Cheson et al 2014) determined by investigator review will be one of the secondary endpoints, together with response in accordance with the Lugano Classification (Cheson et al 2014) determined by IRC using positron emission tomography (PET), progression-free survival (PFS), overall survival (OS), duration of response (DOR), time to response (TTR), time to treatment failure (TTF), time to next line of therapy, patient-reported outcomes (PROs), and safety of zanubrutinib in patients with R/R MZL.

All patients will receive zanubrutinib at 160 mg orally twice daily (two 80-mg capsules orally twice daily), to be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination. Each cycle consists of 28 days.

Study Assessments:

Assessments of MZL status to be performed during the study include: disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen; laboratory studies; bone marrow examination; computed tomography (CT) scan of neck, chest, abdomen, and pelvis with contrast; PET scan; and PROs (5-level EQ-5D version [EQ 5D-5L] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30]).

CT with contrast of neck, chest, abdomen, and pelvis will be performed at screening, at 12, 24, 36, and 48 weeks - followed by every 24 weeks thereafter until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Magnetic resonance imaging (MRI) may be used in patients who have severe allergy to CT contrast, but if used, should be used consistently throughout the study. De-identified copies of all scans will be sent to the IRC facility for tumor response assessment. PET scan will be performed at screening. On a case-by-case basis, the window for the screening PET may be extended after discussion with the medical monitor for patients with IRC-confirmed non-avid disease. For patients with IRC-confirmed PET-avid disease, PET scans will be repeated at 12, 24, 36, 48, and 72 weeks. For patients with PET-avid disease, an assessment of complete response (CR) or progressive disease (PD) must be confirmed by PET scan. Patients should remain on study treatment until disease progression is confirmed by investigator assessment using available radiographic and clinical findings based on the Lugano criteria (Cheson et al 2014).

Bone marrow biopsy and aspirate will be performed at screening and repeated at time of suspected CR for those patients with bone marrow involvement by MZL at screening. For patients with gastrointestinal involvement who had an endoscopy performed during the screening period, a follow up endoscopy is required to confirm CR. Assessments of safety will include adverse events (AEs), serious adverse events (SAEs), laboratory tests, physical examinations, and vital signs. AEs will be graded for severity per the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03).

Key Eligibility Criteria:

Inclusion Criteria

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

1. Age 18 years or older
2. Histologically confirmed diagnosis of MZL including splenic, nodal, and extranodal subtypes (nodal MZL enrollment is capped at 30 patients). Gastric MZL must be H. pylori-negative disease or H. pylori-positive disease that has remained stable, progressed, or relapsed

following antibiotic therapy. Patients with a screening serum immunoelectrophoresis result indicating a monoclonal spike must have a possible diagnosis of Waldenström's macroglobulinemia ruled out.

3. Previously received one or more lines of therapy, including at least one CD20-directed regimen (either as monotherapy or as chemoimmunotherapy), with documented failure to achieve at least PR or documented PD after the most recent systemic treatment
4. Current need for systemic therapy for MZL if, based on the investigator's assessment, the patient has one or more of the following symptoms:
    a. Local symptoms due to progressive or bulky nodal disease
    b. Compromise of normal organ function due to progressive or bulky disease
    c. Presence of systemic B symptoms (ie, fevers, weight loss, night sweats)
    d. Presence of symptomatic extranodal disease, such as effusions
    e. Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism
    f. An increase in disease tempo
5. Availability of archival tissue or consent to obtain fresh tumor tissue sample from an evaluable core or excisional biopsy (approximately 10 to 15 unstained formalin fixed paraffin embedded slides or tissue block).
6. Measurable disease by CT or MRI. Measurable disease is defined as ≥ 1 nodal lesion > 1.5 cm in longest diameter and/or ≥ 1 extranodal lesion > 1.0 cm in longest diameter, and lesion(s) measurable in 2 perpendicular diameters.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
8. Life expectancy ≥ 6 months
9. Adequate bone marrow function
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (growth factor use is allowed), except for patients with bone marrow involvement by MZL in which case ANC must be ≥ 750/mm^3
    b. Platelet ≥ 75,000/mm^3 (may not be post-transfusion), except for patients with bone marrow involvement by MZL in which case the platelet count must be ≥ 50,000/mm^3
10. Adequate organ function
    a. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection)
    b. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase and alanine aminotransferase/serum glutamic pyruvic transaminase ≤ 2.5 × upper limit of normal (ULN) unless due to MZL
    c. Serum total bilirubin < 2.0 × ULN (unless documented Gilbert's syndrome)
11. Female patients of childbearing potential must have a negative pregnancy test at screening and must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib. These methods are described in Section 4.1

12. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception with other methods described above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib
13. Ability to provide written informed consent and can understand and comply with the requirements of the study

Exclusion Criteria

Each patient eligible to participate in this study must not meet any of the following exclusion criteria:

1. Known transformation to aggressive lymphoma, eg, large cell lymphoma. Clinically suspected transformation will require a biopsy of the suspected area prior to enrollment to confirm absence of transformation
2. Clinically significant cardiovascular disease (as defined in Section 4.2)
3. Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
4. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
5. History of stroke or intracranial hemorrhage within 180 days before first dose of study drug
6. Severe or debilitating pulmonary disease
7. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
8. Active fungal, bacterial, and/or viral infection requiring systemic therapy
9. Known central nervous system involvement by lymphoma
10. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs
11. Known infection with HIV, or serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) infection (as defined in Section 4.2)
12. Major surgery within 4 weeks of the first dose of study drug
13. Prior treatment with a Bruton tyrosine kinase (BTK) inhibitor
14. Last dose of prior therapy for MZL ≤ 21 days prior to first dose of study drug, with the following additional exclusion requirements:
    a. Treatment with monoclonal antibody-based therapy within 28 days of first dose of study drug
    b. Treatment with chimeric antigen receptor T-cell therapy within 180 days of first dose of study drug
    c. Treatment with any herbal medicine with anti-neoplastic intent within 28 days of first dose of study drug
    d. Allogeneic hematopoietic stem cell transplantation within 12 months of first dose of study drug

15. Any chemotherapy or radiation treatment for non-MZL indications within 21 days of first dose of study drug
16. Toxicity from prior anti-cancer therapy that has not recovered to ≤ Grade 1 (except for alopecia, ANC, and platelet count; for ANC and platelet count, see Inclusion criterion 9)
17. Pregnant or lactating women
18. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
19. Ongoing alcohol or drug addiction
20. Hypersensitivity to zanubrutinib or any of the other ingredients in zanubrutinib
21. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
22. Received investigational drug within 30 days prior to first dose of zanubrutinib on this study or plans to receive another investigational drug during this study

Test Product, Dose, and Mode of Administration:

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

Reference Therapy, Dose, and Mode of Administration:

None

Statistical Methods:

Analysis Sets:

The safety analysis set includes all patients who were enrolled and received any dose of zanubrutinib. This will be the set of primary interest for safety analyses. The efficacy analysis set consists of all patients in the safety analysis set with confirmed diagnosis of MZL. This set will be the primary analysis set for efficacy analyses. The pharmacokinetic (PK) analysis set includes all patients who have at least one PK sample collected (have at least one post-dose PK concentration) according to the protocol and laboratory manual.

Primary Efficacy Analysis:

The primary efficacy endpoint is ORR according to the Lugano Classification (Cheson et al 2014) as assessed by an IRC. A two-sided Clopper-Pearson 95% confidence interval (CI) for ORR will be calculated.

Assuming 48% ORR of zanubrutinib, a sample size of 65 patients will provide 82% power to rule out an ORR of 30%, at a 1-sided alpha level of 0.025 and using the exact binomial test.

Patients with no postbaseline response assessment will be considered non-responders for the purposes of analysis. The proportion for each response category (CR, PR, stable disease [SD], and PD) will be presented. The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient received the first dose of study drug.

Secondary Efficacy Analysis:

ORR based on the investigator assessment and ORR using PET assessment by IRC will be summarized using same statistical methods employed in the primary efficacy analysis.

PFS is defined as time from study treatment start to PD or death, whichever is earlier. The

Kaplan-Meier method will be used to summarize PFS and corresponding quartiles (including the median). Two-sided 95% CI for the median and other quartiles will be provided. The PFS probability at selected timepoints (eg, 23 weeks) will be estimated along with the corresponding 95% CIs.

OS is defined as time from study treatment start to death due to any cause. Duration of response is defined as time from first response (PR or better) to PD or death, whichever is earlier. The distribution of DOR and OS will be summarized by the Kaplan-Meier method.

TTR, defined as time from study treatment start to first assessment of response (PR or better), will be summarized.

TTF is defined as time from study treatment start to discontinuation of study drug for any reason. The distribution of TTF will be summarized by the Kaplan-Meier method.

Time to next therapy is defined as time from study treatment start to start of first subsequent therapy for MZL. Time to next therapy will be summarized by the Kaplan-Meier method.

PROs (value and change from baseline) will be summarized for each assessment timepoint.

Exploratory Efficacy Analysis:

ORR in accordance with Cheson et al 1999 as determined by the IRC will be summarized using the same statistical methods employed in the primary efficacy analysis.

Safety Analysis:

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities terms and graded according to the NCI CTCAE v4.03 (NCI 2010). A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug and for up to 30 days following study drug discontinuation or the start of new anti-cancer therapy, whichever comes first. TEAEs of any grade, SAEs, TEAEs of grade 3 or above, TEAEs leading to treatment discontinuation, dose reduction, or dose interruption, TEAEs leading to death, treatment-related TEAEs, and TEAEs of special interest will be summarized. TEAEs will also be summarized by system organ class (SOC), preferred term (PT), and worst grade.

Multiple occurrences of the same event will be counted once at the maximum severity within a SOC and PT.

Deaths and cause of deaths will be summarized.

Laboratory data with values outside of the normal range will be identified. Selected laboratory data will be summarized by grade. Change of baseline to the worst post-baseline grade will be provided. Vital signs, electrocardiograms, and ECOG will be summarized by visit and change from baseline will be provided if necessary.

Sample Size:

Assuming a null hypothesized ORR of 30%, a sample size of 65 patients will provide 82% power for the alternative ORR of 48%, at a 1-sided alpha level of 0.025 and using the exact binomial test. The alternative ORR is based on the observed ORR for the ibrutinib study in R/R MZL (Noy et al 2017). For an observed ORR of 48% (31/65), the 95% exact binomial confidence interval is (35%, 60%).

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton tyrosine kinase
CBC	complete blood count
CI	confidence interval
C_{max}	maximum plasma concentration
CR	complete response
CRu	complete remission unconfirmed
CT	computed tomography
CYP	cytochrome P450
CYP3A	strong cytochrome P450, family 3, subfamily A
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLC-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EQ 5D-5L	5-level EQ-5D version
FDA	Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
IC_{50}	50% maximum inhibitory concentration
IEC	independent ethics committee
IRB	institutional review board
IRC	Independent Review Committee

Abbreviation	Definition
MALT	mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PBPK	physiologically based pharmacokinetics
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT interval
R/R MZL	relapsed or refractory marginal zone lymphoma
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TTF	time to treatment failure
TTR	time to response
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is an indolent non-Hodgkin lymphoma (NHL) that originates from memory B lymphocytes normally present in the marginal zone of secondary lymphoid follicles within the spleen, lymph nodes, and mucosal lymphoid tissues (Kahl and Yang 2008). Despite having a common origin in the marginal zone of the B-follicle, there are distinct clinical and molecular characteristics of MZLs originating at different anatomic sites. As such, MZLs are categorized by the World Health Organization into 3 distinct subtypes, which include extranodal MZL mostly represented by mucosa-associated lymphoid tissue (MALT) lymphoma, nodal MZL, and splenic MZL. Marginal zone lymphomas comprise about 5% to 17% of all NHLs in adults, with MALT lymphoma being the most common subtype, occurring in approximately 50% to 70% of MZLs and 7% to 8% of all NHLs, followed by splenic MZL (20% of all MZLs), and nodal MZL (10% of all MZLs). Median age at diagnosis varies between these MZL subtypes, ranging from 50 to 69 years, with an overall greater incidence reported in men compared with women (Sriskandarajah and Dearden 2017). MZL incidence rates are higher among men than women for the stomach, small intestine, skin, and kidney, while the reverse is reported for MZLs involving the salivary gland, soft tissue, and thyroid (Khalil et al 2014).

Marginal zone lymphomas can occur at any extranodal site, with the stomach being the most common site. Additional extranodal sites may include, but are not limited to, the ocular adnexa, lung, skin, thyroid, and salivary glands. Extranodal MZLs are frequently associated with chronic inflammation and infectious agents that can give rise to chronic infections, such as *Helicobacter pylori* in gastric extranodal MZL, *Chlamydophila psittaci* in ocular adnexa extranodal MZL, *Campylobacter jejuni* in immunoproliferative small intestinal disease, and *Borrelia burgdorferi* in cutaneous extranodal MZL. Autoimmune conditions that may be associated with development of MZLs include Sjögren syndrome, lymphoepithelial sialadenitis, and Hashimoto thyroiditis (Schreuder et al 2017).

1.1.1. Mucosa-associated Lymphoid Tissue Lymphoma

For MALT lymphomas, the gastrointestinal tract is the most common site of involvement and represents about 50% of all MALT lymphomas. Within the gastrointestinal tract, the stomach is the most common primary site, with the orbit (7% to 12%), lung (8% to 14%), and skin (9% to 12%) representing the other common non-gastrointestinal primary sites (Nathwani et al 1999; Thieblemont et al 1997; Zucca et al 2003). Gastric MALTs are typically associated with a longer time to progression and progression-free survival (PFS) than non-gastric MALTs, although 10-year overall survival (OS) is similar between gastric and non-gastric MALTs (Thieblemont et al 1997; Ueda et al 2013).

Chromosomal translocations implicated in the pathogenesis of MALT lymphomas include t(11;18) with the resultant formation of the chimeric fusion gene API2-MALT1, and t(1;14) with the resultant over-expression of BCL10 protein. The abnormality t(1;14) has been detected in MALT lymphomas of the stomach, lung, and skin, whereas the t(11;18) is frequently detected in gastric and pulmonary MALT lymphomas (Auer et al 1997; Murga Penas et al 2003; Willis et al 1999). Both t(11;18) and BCL10 over-expression are associated with locally advanced disease and tend to be less responsive to *Helicobacter pylori* eradication therapy

(Liu et al 2001). In addition, t(14;18) has also been reported in MALT lymphomas with a resultant deregulated expression of the MALT1 gene (Murga Penas et al 2003; Streubel et al 2003) and t(3;14), leading to upregulation of the FOXP1 gene (Streubel et al 2003). The clinical significance of t(14;18) and t(3;14) is unclear.

Common presenting symptoms of gastric MALT include dyspepsia, reflux, abdominal pain, nausea, and weight loss (Kahl and Yang 2008). Endoscopic biopsy is essential for establishing the diagnosis of gastric MALT lymphoma. *Helicobacter pylori* plays a key role in the pathogenesis of gastric MALT lymphoma, with eradication of the bacteria efficacious towards tumor regression in approximately 70% of patients (Isaacson and Spencer 1996; Wotherspoon 1998; Kuo et al 2017). Approximately 5% to 10% of gastric MALT lymphoma will be negative for *Helicobacter pylori* infection, with translocation t(11;18) frequently predicting *Helicobacter pylori* negative or antibiotic resistant disease. Hence, molecular analysis by polymerase chain reaction (PCR) or fluorescent in situ hybridization for assessment of t(11;18) may be considered at initial diagnosis to inform treatment decisions. In general, *Helicobacter pylori* eradication therapy comprises a proton pump inhibitor and a combination of antibiotics such as clarithromycin and amoxicillin, or metronidazole for those allergic to penicillin. The regimen of antibiotics should be based upon the prevalence of clarithromycin-resistant strains in the population and upon a patient's previous exposure to macrolide antibiotics (Zagari et al 2017).

Treatment for MALT lymphoma depends upon the location and stage of disease. For localized gastric MALT lymphoma positive for *Helicobacter pylori* infection, a trial of antibiotic is recommended. For those with chromosomal aberrations such as t(11;18) that predicts for lack of response to antibiotics, radiation therapy may be considered. Rituximab is an option for patients with contraindications to radiation therapy (Martinelli et al 2005). For patients with non-gastric MALT lymphoma that comprises about 70% of MALT lymphomas, radiation therapy is recommended for those with stage I or II disease, with rituximab being an option for selected patients. For those with localized disease in the lung, thyroid, colon, small intestine, or breast, surgical excision for adequate diagnosis may be an appropriate treatment option, followed by postoperative locoregional radiotherapy for surgical margin-positive disease.

For those with advanced stage disease (stage III or IV), treatment is commonly approached with regimens used for other indolent NHLs such as follicular lymphoma, with initiation of treatment guided by end-organ dysfunction or the presence of symptoms, bulky disease at presentation, or steady progression of disease. Close monitoring is an acceptable option for asymptomatic patients without indication for treatment. For those in need of treatment, potential treatment options are systemic therapy with either single chemotherapy agent or combination chemotherapy regimens; single-agent anti-CD20 monoclonal antibody; or chemoimmunotherapy.

1.1.2. Nodal Marginal Zone Lymphoma

Peripheral lymphadenopathy is present in nearly all cases of nodal MZL (> 95%), with thoracic or intra-abdominal lymphadenopathy detected in about 50% of patients. Bone marrow involvement is seen in approximately 30% to 40% of cases. Median age of diagnosis is between 50 and 62 years. Most presentations tend to be non-bulky lymphadenopathy, and B-symptoms are present in only about 15% of patients (Nathwani et al 1999; Berger et al 2000). Long-term

outcome of nodal MZL tends to be less favorable compared with MALT lymphomas (Nathwani et al 1999). Nodal MZL primarily occurs in the lymph nodes, but involvement of additional extranodal sites is common. Diagnosis of nodal MZL requires careful evaluation to rule out extranodal primary disease, and must be pathologically distinguished from nodal follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and chronic lymphocytic leukemia, all of which are more common than MZL.

In the lymph nodes, the pattern of tumor growth may be perivascular, perisinusoidal, or perifollicular, possibly with invasion of malignant cells into the follicles in a pattern known as follicular colonization. Alternatively, the growth pattern may be nodular with expansion of the marginal zone and destruction of the mantle zone surrounding the germinal center of the follicle. Median age of diagnosis for nodal MZL is 60 years, and the disease tends to present in advanced stage with widespread, non-bulky lymphadenopathy. A small to moderate immunoglobulin M paraprotein can be detected in approximately 10% of patients (Kahl and Yang 2008).

Treatment options in general follow the principles applied for follicular lymphoma or small lymphocytic lymphoma. Close observation is appropriate for asymptomatic patients with low tumor burden, or single-agent rituximab for those unwilling to undergo a watch-and-wait approach or for elderly patients who are not candidates for chemotherapy. Front-line systemic therapy for those in need of treatment may include combination cyclophosphamide, vincristine, prednisone; cyclophosphamide, doxorubicin, vincristine, prednisone; or a purine analogue such as fludarabine, in combination with rituximab. Approved or experimental treatment options for relapsed or refractory (R/R) disease might include Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib; PI3K/AKT/mTOR inhibitors such as everolimus (Conconi et al 2014) and idelalisib (Gopal et al 2014); immunomodulators such as lenalidomide (Kiesewetter et al 2013; Fowler et al 2014); and proteasome inhibitors such as bortezomib, although the high rate of neuropathy with bortezomib limits the clinical usefulness of this agent in patients (Thieblemont et al 2016).

1.1.3. Splenic Marginal Zone Lymphoma

Patients with splenic MZL present with splenomegaly in all cases, while peripheral lymphadenopathy is generally not detected. Splenic hilar lymphadenopathy may be present, and involvement of thoracic or abdominal nodes may be seen in about a third of patients with splenic MZL (Arcaini et al 2004; Berger et al 2000). Median age of diagnosis is 65 years, with diagnosis being most definitive at splenectomy. Prognosis is usually good, with median survival around 10 to 15 years (Arcaini et al 2016; Thieblemont et al 2016), but some degree of heterogeneity exists with 5% to 10% of patients presenting with more aggressive disease and shorter survival (Thieblemont 2017).

Viral hepatitis C (HCV) has been implicated in the pathogenesis of splenic MZL, with the E2 glycoprotein of HCV interacting with CD81 in the B cells, leading to B-cell activation via the B-cell receptor (BCR) and increased proliferation (Thieblemont 2017). In one retrospective study, positive HCV serology was detected in 35% of splenic MZL patients (Arcaini et al 2004), while in other studies, it was reported as < 10%. Geography is an important influencing factor, with the highest association between splenic MZL and HCV reported in Japan and northern Italy (Satoh et al 1997; Arcaini et al 2007). Most common presenting symptom of splenic MZL is abdominal discomfort due to splenomegaly, along with modest cytopenias secondary to splenic

sequestration coupled with a smaller contribution from marrow infiltration. In a multivariate model, risk factors associated with an inferior OS for splenic MZL were hemoglobin (Hgb) < 12 g/dL, albumin < 3.5 g/dL, and lactate dehydrogenase > upper limit of normal (ULN). Three risk groups were subsequently identified using this model: low risk (0 factor), intermediate risk (1 factor), high risk (2 to 3 factors), with 5-year cause-specific survival of 88%, 73%, and 50%, respectively (Arcaini et al 2006).

Front-line antiviral therapy with interferon-alfa or pegylated interferon, with or without ribavirin, has been shown to induce virologic and hematologic response in some patients with HCV-positive MZL including splenic MZL, and it represents an appropriate treatment option (Arcaini et al 2011). For those with symptomatic splenomegaly, they can be further managed with splenectomy or rituximab. For those with HCV-negative disease, treatment options include splenectomy, single agent or combination chemotherapy, single-agent rituximab, or chemoimmunotherapy. Splenectomy alone can result in overall response rate (ORR) of 80% to 90%, with a median OS of 93 months (Iannitto et al 2004; Milosevic et al 2009), while splenectomy followed by adjuvant chemotherapy is associated with a complete remission (CR) rate of 50%, and a median OS of about 9 years (Chacon et al 2002; Milosevic et al 2009). For patients who are candidates for splenectomy, pneumococcal and meningococcal vaccination should be administered at least 2 weeks prior to surgery. For patients who are too frail for splenectomy, palliative splenic radiation or systemic chemotherapy can be considered.

For those with R/R disease, management options are as described above for R/R nodal MZL (Section 1.1.2).

1.2. B-cell Receptor Signaling

The BCR exists as a protein complex in the plasma membrane of B-cells and belongs to a small family of receptors which includes the T-cell receptor and receptors for the fragment crystallizable regions of immunoglobulin E and immunoglobulin G (Burrows and Cooper 1997). The BCR is essential for normal B-cell development and maturation and is implicated as a pivotal pathway in tumorigenesis. BTK is a member of the TEC kinase family that also includes TEC, ITK, and BMX/ETK, and is a non-receptor tyrosine kinase that is recruited early in the BCR signaling cascade in conjunction with SYK and PI3Kδ (Niemann and Wiestner 2013). BTK appears to be essential only in B-cells, and is required for BCR-induced calcium release, cell proliferation, and activation of the NF-κB pathway (Buggy and Elias 2012; Honigberg et al 2010). It is also involved in regulating actin dynamics and antigen processing during BCR activation (Sharma et al 2009), as well as B-cell trafficking mediated by the chemokine receptors CXCR4 and CXCR5 (de Gorter et al 2007).

BCR signaling has been proposed to be a key activation pathway in MZL. Development of MZL is often associated with chronic infectious agents like HCV and *Helicobacter pylori* that may lead to antigen-mediated BCR activation, a potential driver of lymphomagenesis (Noy et al 2017). Particularly, in a subset of splenic MZL, the lymphoma cells express a BCR that can bind to the E2 envelope protein of HCV, suggesting these lymphoma cells arise as an expansion of HCV-reactive B-cells. In gastric MALT lymphomas, association with *Helicobacter pylori* is well-established, suggesting inflammation as well as direct antigenic drive may contribute to lymphomagenesis. Hence, BCR pathway inhibitors are rapidly becoming an important treatment option for NHLs, with approval granted by the United States (US) Food and

Drug Administration (FDA) to ibrutinib, a BTK inhibitor, for treatment of various lymphoma conditions including R/R MZL.

1.2.1. Ibrutinib

Ibrutinib is a small molecule inhibitor of BTK. Nonclinical studies have demonstrated inhibition of malignant B-cell proliferation and survival by ibrutinib in vivo, as well as cell migration and substrate adhesion in vitro. In patients with recurrent B-cell lymphoma, > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

A Phase 2 study of ibrutinib was conducted in patients with R/R MZL (n=63) (NCT01980628) with at least 1 prior therapy for MZL that included at least one CD20-directed regimen, administered as either monotherapy or as chemoimmunotherapy. Patients were also required to have documented failure to achieve at least partial response (PR) or had progressive disease (PD) after the most recent systemic therapy. Study treatment was ibrutinib 560 mg orally once daily until disease progression or unacceptable toxicity for up to 3 years. Primary endpoint was ORR assessed by Independent Review Committee (IRC), and in accordance with adaptation of the 2007 International Working Group Criteria (Cheson et al 2007). In addition to computed tomography (CT) scan, positron emission tomography (PET) scan was required for pretreatment tumor assessment at screening for all patients, and for confirmation of complete response (CR) for those with a positive pretreatment PET scan. Among the 63 patients, 32 (51%) had extranodal MZL, 14 (22%) had splenic MZL, and 17 (27%) had nodal MZL. Bone marrow involvement was reported in 21 patients (33%). Extranodal sites of involvement were reported in 36 patients (57%), and included lung, pleural effusion, extrapleural involvement, subcutaneous/soft tissue, liver, orbit, pericardium, bowel, ascites, parotid, renal, spleen, and retroperitoneum. The median number of prior systemic therapies was 2 (range 1 to 9), with 35% of patients receiving ≥ 3 prior therapies. Seventeen patients (27%) received only rituximab monotherapy, 40 patients (63%) received ≥ 1 CD20-directed chemoimmunotherapy, and 6 patients (10%) received systemic treatment with other targeted agents or chemotherapy prior to or following rituximab containing therapy. Two patients (3%) had undergone prior autologous hematopoietic stem cell transplantation, and 14 patients (22%) were refractory to their most recent systemic therapy (Noy et al 2017).

Among the 63 patients, 3 patients were deemed to have non-measurable disease at baseline by independent review, and hence, only 60 patients were evaluable for efficacy. ORR per IRC was 48% (95% confidence interval [CI], 35-62), with CR achieved by 2 patients (3%). Per investigator review, ORR was 53% (95% CI, 40-66), with CR achieved by 4 patients (7%). With clinical benefit defined as stable disease (SD) or better, 83% had clinical benefit per IRC, and 88% per investigator review (Noy et al 2017). ORR by MZL subtype were 46.9%, 41.2%, and 50% for MALT, nodal, and splenic MZL, respectively (Imbruvica® US Prescribing Information). Median time to response (TTR) was 4.5 months (range 2.3 to 16.4), and median time to best response was 5.2 months (range 2.3 to 16.4). Response was consistent across disease characteristics, ie, MZL subtype, age (< 65 or ≥ 65), baseline ECOG (0 or ≥ 1), tumor size (> or ≤ 6 cm), presence or absence of extranodal disease, bone marrow involvement, prior number of regimens (1, 2, or ≥ 3), prior chemoimmunotherapy (yes or no), and prior rituximab only. With a median follow-up of 19.4 months (95% CI, 17.6-22.3), median PFS was 14.2 months (95% CI,

8.3 to not estimable) per IRC, and 15 months (95% CI, 12 to not estimable) per investigator assessment. In terms of PFS by MZL subtype, extranodal MZL was 13.8 months (95% CI, 8.3 to not estimable), splenic MZL was 19.4 months (95% CI, 8.2 to not estimable), and nodal MZL was 8.3 months (95% CI, 2.8 to not estimable). OS rate at 18 months was estimated to be 81% (95% CI, 68-89), and median OS was not reached. Confirmed pseudoprogression occurred in 2 patients at Weeks 9 and 13, respectively (Noy et al 2017).

The most common ≥ Grade 3 treatment-emergent AEs (TEAEs) for the Phase 2 ibrutinib MZL study (NCT01980628) were anemia (14%), pneumonia (8%), and fatigue (6%). SAEs of any grade occurred in 28 patients (44%), with Grade 3 or 4 pneumonia being the most common event reported in 5 patients (8%). Thirty-seven patients (59%) reported a bleeding AE, with 1 bleeding AE resulting in death (Grade 5 cerebral hemorrhage) for a patient anticoagulated with the low molecular weight heparin dalteparin. The cerebral hemorrhage occurred 19 days after discontinuation of ibrutinib and was attributed by the investigator as unlikely related to ibrutinib. Atrial fibrillation was reported in 4 patients (6%), all Grade 1 or 2, and did not lead to dose adjustment or treatment discontinuation. Diarrhea was the most common AE leading to treatment discontinuation, occurring in 3% of patients (Noy et al 2017). All grades diarrhea occurred in 43% of MZL patients, with 5 patients reported to have experienced ≥ Grade 3 diarrhea (Imbruvica® US Prescribing Information). Across ibrutinib clinical trials, ≥ Grade 3 bleeding events occurred in 6% of patients; atrial flutter and atrial fibrillation occurred in 6% to 9% of patients (particularly in patients with cardiac risk factors, hypertension, acute infection, and a previous history of atrial fibrillation) (Imbruvica® US Prescribing Information).

Ibrutinib is currently approved by US FDA for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia/small lymphocytic lymphoma with or without 17p deletion, patients with Waldenström macroglobulinemia, patients with marginal zone lymphoma who have received at least 1 prior anti-CD20 based therapy, and patients with chronic graft versus host disease after failure of 1 or more lines of systemic therapy (Imbruvica® US Prescribing Information).

1.3. Zanubrutinib

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

1. Zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, including EGFR, FGR, FRK, HER2, HER4, ITK, JAK 3, LCK, and TEC, which may reduce toxicities possibly due to off-target inhibition such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue.
2. Zanubrutinib has improved oral bioavailability.
3. Zanubrutinib displays significantly less inhibitory effect on rituximab-induced, antibody-dependent, cell-mediated cytotoxicity, and so is unlikely to adversely impact the antitumor effects of rituximab.

Zanubrutinib (BRUKINSA™) is approved by the US FDA under accelerated approval for the treatment of adult patients with MCL who have received at least one prior therapy.

1.3.1. Nonclinical Data for Zanubrutinib

Summaries of nonclinical studies are provided below. For more detailed information please refer to the zanubrutinib Investigator's Brochure (BGB-3111 Investigator's Brochure).

Zanubrutinib is a potent, specific, and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nM. Cellular assays confirm that zanubrutinib inhibits BCR aggregation-triggered BTK autophosphorylation and blocks downstream phospholipase C gamma 2 signaling in mantle cell lymphoma cell lines. Zanubrutinib had an IC_{50} of 1.8 nM in a homogeneous time-resolved fluorescence-based BTKpY223 assay. It potently and selectively inhibited cellular growth of several mantle cell lymphoma cell lines (REC-1, Mino and JeKo-1), and the activated B-cell type diffuse large B-cell lymphoma cell line TMD-8, with IC_{50} values from 0.36 nM to 20 nM while it was inactive in many other hematologic cancer cell lines.

In vivo studies have demonstrated that zanubrutinib is significantly more effective than ibrutinib when inducing dose-dependent antitumor effects against REC-1 mantle cell lymphoma xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib also demonstrated better antitumor activity than ibrutinib in TMD-8 diffuse large B-cell lymphoma subcutaneous xenograft model. In a PK/pharmacodynamics study, oral administration of zanubrutinib resulted in time-dependent occupancy of BTK in blood and in spleen in mice and was approximately 3-fold more potent than ibrutinib in mouse pharmacodynamic assays.

In a panel of 342 human kinases, 1 μM zanubrutinib inhibited only 12 other kinases by > 70%. Zanubrutinib was more selective than ibrutinib for inhibition of kinase activity of BTK EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antibody-dependent cell-mediated cytotoxicity. Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity, consistent with zanubrutinib being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays.

The toxicity profiles of zanubrutinib have been well characterized in rats and dogs. No specific safety concerns were identified in vital organs/systems, including cardiovascular system, respiratory system, and central nervous systems. No corrected QT interval (QTc) changes were noted in the conscious telemetry-implanted dogs over 24 hours after dosing up to 100 mg/kg, or in the repeat dose toxicity studies in dogs over 91 days at doses up to 100 mg/kg/day. No mortality or severe toxicity was noted in 91-day repeat dose toxicity studies in either rats or dogs at doses up to 300 mg/kg and 100 mg/kg, respectively. Test article-related reversible histopathology changes were mainly noted in rats, including pancreas, spleen, prostate gland, cecum, colon, rectum, skin (lip and/or nose), and uterus. None of the above findings was considered to be adverse in the 91-day repeated dosing studies. No genotoxicity was noted in the genotoxicity core battery studies.

1.3.2. Summary of Relevant Clinical Experience with Zanubrutinib

1.3.2.1. Dose Selection for Zanubrutinib

Dose selection was based on results from the Phase 1 dose-finding Study BGB-3111-AU-003, which evaluated the PK/pharmacodynamics, safety, and preliminary efficacy of zanubrutinib at doses from 40 mg to 320 mg once a day and 160 mg twice a day. A maximum tolerated dose (MTD) was not reached in Study BGB-3111-AU-003, and no dose-limiting toxicity (DLT) was observed during the dose escalation part of the study.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice daily and 320 mg once daily (Tam et al 2015). At the 160 mg twice daily dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström macroglobulinemia and follicular lymphoma) at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive experience at the 160 mg twice daily and 320 mg once daily doses, with both schedules showing a high level of activity without compromise of the tolerability profile as compared to lower doses of zanubrutinib. Therefore, 160 mg administered orally twice daily has been selected as the recommended Phase 2 dose based on sustained target occupancy, high rates of objective response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

1.3.2.2. Clinical Pharmacology

In the first-in-human, Phase 1 study, BGB-3111-AU-003, the PK of zanubrutinib was linear between 40 mg and 320 mg once a day administered orally. The absorption of zanubrutinib is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 2 to 4 hours. Results from a food effect study (BGB-3111-103) showed that dosing with food (high-fat or low-fat meal) did not cause any significantly meaningful effects on the AUC of zanubrutinib and, therefore, zanubrutinib can be administered with or without food.

The QT interval prolongation potential of zanubrutinib was evaluated in healthy patients 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.

A dedicated hepatic impairment study (BGB-3111-107) showed that there was no substantial difference in PK between patients with mild/moderate hepatic impairment and healthy subjects. The total and unbound plasma exposures (AUC) of zanubrutinib in subjects with severe hepatic impairment were 1.60- and 2.9-fold higher in subjects with severe hepatic impairment compared to healthy controls.

Results from a dedicated 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 C_{max}, in healthy patients. 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, a physiologically based pharmacokinetics (PBPK) model was developed and used to predict the effect of moderate CYP3A inhibitors and CYP3A inducers on the PK of zanubrutinib. PBPK simulations 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), BCRP (rosuvastatin) using a cocktail approach. The results showed that zanubrutinib does not affect drugs metabolized by CYP2C9 (warfarin) or transported by BCRP (statins). Zanubrutinib had a weak induction effect on CYP3A and CYP2C19 enzymes. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib. Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}.

For more detailed information on the clinical experience for zanubrutinib, please refer to the zanubrutinib Investigator's Brochure (BGB-3111 Investigator's Brochure).

1.3.2.3. Benefit-Risk Assessment

As of 31 August 2019, over 1500 patients have received zanubrutinib in B-cell malignancies either as monotherapy or in combination with another agent. Historically, the class of BTK inhibitors has raised some safety concerns, particularly regarding the potential for serious hemorrhage and cardiac rhythm disturbance with atrial fibrillation or flutter being the most common events. The pooled analysis of zanubrutinib safety data showed that 1.9% of patients had atrial fibrillation and atrial flutter in the combined database of 682 patients with hematological malignancies who were treated with zanubrutinib monotherapy. Major hemorrhages including serious or ≥ Grade 3 bleeding events have been reported in 2.5% of these patients. Concomitant use of vitamin K antagonists was, and continues to be, allowed in zanubrutinib trials. No new safety or tolerability signals have been observed and there have been few instances of drug discontinuation due to AEs (Tam et al 2019a).

Efficacy data for zanubrutinib monotherapy are available from the BGB-3111-AU-003 study. This is an ongoing global first-in-human, Phase 1, open-label, multiple-dose, dose-escalation and dose-expansion study of zanubrutinib that was initiated in Australia in August 2014. As of 31 August 2019, 385 patients had been dosed in this clinical study (BGB-3111 Investigator's Brochure).

Of the 84 NHL patients evaluable for response, the ORR was 59.5% (50/84) overall, 62% (36/58) in the aggressive lymphoma (AL) group (DLBCL and MCL), and 54% (14/26) in the indolent lymphoma (IL) group (FL and MZL). Most responses were partial responses: 41.7% (35/84) overall, 41% (24/58) in the AL group, and 42% (11/26) in the IL group. Stable disease was seen in 14/84 (16.7%) of patients overall. Fifteen patients progressed by the first response assessment (14 in the AL group and 1 in the IL group). By comparison, in the single-arm, open-label, Phase 2 DAWN study of ibrutinib monotherapy in R/R indolent lymphoma patients (Gopal et al 2016), the ORR was 21%. Updated results in 48 response-evaluable patients with MCL as of the data cut-off date of 13 Dec 2018 (Tam et al 2019b) showed an ORR of 85.4% (41/48), with a CR rate of 29.2% (14/48). The overall duration of response (DOR) was 16.2 months (95% CI, 11.5-28.2).

Among the 20 patients with R/R MZL enrolled in the BGB-3111-AU-003 study (Tedeschi et al 2020), the ORR was 75% (15/20), with a CR rate of 10% (2/20). The median DOR (complete or partial response) was not reached (95% CI, 6.47 months to not evaluable) at a median response follow-up of 12 months. One patient discontinued zanubrutinib due to an AE of diarrhea. One patient experienced Grade 3 hemoptysis. There were no cases of atrial fibrillation/flutter.

Thus, available data for zanubrutinib in patients with indolent B-cell lymphoma support a positive benefit-risk profile for this drug as an investigational agent in treatment of marginal zone lymphoma.

2. STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of zanubrutinib in R/R MZL as measured by ORR in accordance with the Lugano Classification (Cheson et al 2014) (Appendix 2) determined by the Independent Review Committee (IRC)

Secondary:

- To evaluate the efficacy of zanubrutinib in R/R MZL in accordance with the Lugano Classification (Cheson et al 2014) (Appendix 2) as measured by the following:
  - Overall response rate determined by investigator assessment
  - Progression-free survival determined by IRC and by investigator
  - Overall survival
  - Duration of response determined by IRC and by investigator
  - Time to response determined by IRC and by investigator
  - Time to treatment failure
  - Time to next line of therapy for MZL
- To evaluate patient-reported outcomes (PROs)
- To determine the safety of zanubrutinib
- To determine PK parameters of zanubrutinib

Exploratory:

- Overall response rate in accordance with Cheson et al 1999 as determined by the IRC

3. STUDY DESIGN

3.1. Study Rationale

BCR signaling regulates multiple cellular processes, including proliferation, differentiation. It has also been proposed to be a key activation pathway in MZL. BTK is a non-receptor tyrosine kinase that is recruited early in the BCR signaling cascade in conjunction with SYK and PI3Kδ (Niemann and Wiestner 2013), and inhibitors of BTK are rapidly becoming an important treatment option for NHLs.

Ibrutinib, a US FDA-approved, first-generation BTK inhibitor that blocks BCR signaling in human B cells via specific active site occupancy, has been shown to be efficacious in the treatment of MZL (Section 1.2.1).

Preliminary efficacy data from the Phase 1 BGB-3111-AU-003 study of zanubrutinib in patients with B-cell malignancy revealed an ORR (CR + PR) of 78% in patients with R/R MZL (n = 9), with all responses being PR. Most frequent AEs for the MZL patients were 3 patients with nausea (30%), 3 patients with petechiae/purpura/contusion (30%), 3 patients with upper respiratory tract infection (30%), 2 patients with diarrhea (20%), 2 patients with headache (20%), 2 patients with pyrexia (20%), 2 patients with rash (20%), 1 patient with hypertension (10%), and 1 patient with non-cardiac chest pain (10%). There was 1 event of drug-related SAE of diarrhea (10%) and no Grade 5 event for the MZL patients. There was no atrial fibrillation reported for the MZL patients (Tam et al 2017).

Treatment with zanubrutinib has been well-tolerated across all studies thus far. Compared with ibrutinib, zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, possibly leading to reduced toxicities due to off-target inhibition such as diarrhea, thrombocytopenia, bleed, atrial fibrillation, rash, and fatigue. The preliminary data from study BGB-3111-AU-003 shows 7 out of 9 patients demonstrated overall response (ORR of 78%). Preliminary safety data from the BGB-3111-AU-003 study also revealed a tolerable and safe profile for zanubrutinib in MZL, with possibly a lower rate of AEs of Special Interest such as atrial fibrillation and bleed when compared with ibrutinib. In view of these findings, a Phase 2, open-label study evaluating the efficacy of zanubrutinib in patients with R/R MZL as measured by the primary endpoint ORR will be conducted.

3.2. Summary of Study Design

This is a Phase 2, open-label, single-arm study of zanubrutinib in approximately 65 patients with R/R MZL. The primary efficacy endpoint is ORR (CR + PR) in accordance with the Lugano Classification (Cheson et al 2014) (Appendix 2) determined by IRC. Efficacy in accordance with the Lugano Classification determined by investigator review will be one of the secondary endpoints together with PFS, OS, duration of response (DOR), TTR, time to treatment failure (TTF), time to next line of therapy for MZL, PRO, and safety of zanubrutinib.

All patients will receive zanubrutinib at 160 mg orally twice daily (two 80-mg capsules orally twice daily), to be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination. Each cycle consists of 28 days.

3.2.1. Study Assessments

Assessments of MZL status to be performed during the study include: disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen; laboratory studies; bone marrow examination; CT scan of neck, chest, abdomen, and pelvis with contrast; PET scan; patient-reported outcomes (PROs) (5-level EQ-5D version [EQ-5D-5L], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30]).

Imaging of the neck, chest, abdomen, and pelvis by CT with contrast will be performed at screening, at 12, 24, 36, and 48 weeks - followed by every 24 weeks thereafter until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Magnetic resonance imaging (MRI) may be used in patients who have severe allergy to CT contrast, but if used, should be used consistently throughout the study. A PET scan will be performed at screening and repeated for those with PET-avid disease at 12, 24, 36, 48, and 72 weeks. On a case-by-case basis, the window for the screening PET may be extended after discussion with the medical monitor for patients with IRC-confirmed non-avid disease. For patients with PET-avid disease, an assessment of CR or PD must be confirmed by PET scan. De-identified copies of all scans will be sent to the IRC facility for tumor response assessment.

Patients should remain on study treatment until disease progression is confirmed by investigator assessment using available radiographic and clinical findings based on the Lugano criteria (Cheson et al 2014).

Bone marrow biopsy and aspirate will be performed at screening and repeated at time of suspected CR for those patients who had bone marrow involvement by MZL at screening.

For patients with gastrointestinal involvement who had an endoscopy performed during the screening period, a follow up endoscopy is required to confirm CR.

Assessments of safety will include AEs, SAEs, laboratory tests, physical examinations, and vital signs. AEs will be graded for severity per the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03).

3.3. Blinding

Treatment with zanubrutinib is open-label.

4. ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

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

1. Age 18 years or older
2. Histologically confirmed diagnosis of MZL including splenic, nodal, and extranodal subtypes (nodal MZL enrollment is capped at 30 patients). Gastric MZL must be H. pylori-negative disease or H. pylori-positive disease that has remained stable, progressed, or relapsed following antibiotic therapy. Patients with a screening immunoelectrophoresis result indicating a monoclonal spike must have a possible diagnosis of Waldenström's macroglobulinemia ruled out.
3. Previously received one or more lines of therapy, including at least one CD20-directed regimen (either as monotherapy or as chemoimmunotherapy), with documented failure to achieve at least PR or documented PD after the most recent systemic treatment
4. Current need for systemic therapy for MZL if, based on the investigator's assessment, the patient has one or more of the following symptoms:
    a. Local symptoms due to progressive or bulky nodal disease
    b. Compromise of normal organ function due to progressive or bulky disease
    c. Presence of systemic B symptoms (ie, fevers, weight loss, night sweats)
    d. Presence of symptomatic extranodal disease, such as effusions
    e. Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism
    f. An increase in disease tempo
5. Availability of archival tissue or consent to obtain fresh tumor tissue sample from an evaluable core or excisional biopsy (approximately 10 to 15 unstained formalin fixed paraffin embedded slides or tissue block).
6. Measurable disease by CT or MRI. Measurable disease is defined as ≥ 1 nodal lesion > 1.5 cm in longest diameter and/or ≥ 1 extranodal lesion > 1.0 cm in longest diameter, and lesion(s) measurable in 2 perpendicular diameters.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
8. Life expectancy ≥ 6 months
9. Adequate bone marrow function as defined by:
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (growth factor use is allowed), except for patients with bone marrow involvement by MZL in which case ANC must be ≥ 750/mm^3
    b. Platelet ≥ 75,000/mm^3 (may not be post-transfusion), except for patients with bone marrow involvement by MZL in which case the platelet count must be ≥ 50,000/mm^3

10. Adequate organ function defined as:
    a. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection)
    b. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase and alanine aminotransferase/serum glutamic pyruvic transaminase ≤ 2.5 × ULN unless due to MZL
    c. Serum total bilirubin < 2.0 × ULN (unless documented Gilbert's syndrome)
11. Female patients of childbearing potential must have a negative pregnancy test at screening and must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib. These methods include the following:
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
        – Oral, intravaginal, or transdermal
    b. Progestogen-only hormonal contraception associated with the inhibition of ovulation
        – Oral, injectable, or implantable
    c. An intrauterine device
    d. Intrauterine hormone-releasing system
    e. Bilateral tubal occlusion
    f. Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
    g. 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 zanubrutinib. Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, 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.
    If you are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used.
    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single high follicle stimulating hormone measurement is insufficient.

12. Male patients are eligible if abstinent (as defined above), vasectomized or if they agree to the use of barrier contraception with other methods described above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib.
13. Ability to provide written informed consent and can understand and comply with the requirements of the study

4.2. Exclusion Criteria

Each patient eligible to participate in this study must not meet any of the following exclusion criteria:

1. Known transformation to aggressive lymphoma, eg, large cell lymphoma. Clinically suspected transformation will require a biopsy of the suspected area prior to enrollment to confirm absence of transformation
2. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within 6 months before screening
    b. Unstable angina within 3 months before screening
    c. New York Heart Association class III or IV congestive heart failure (Appendix 3)
    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes)
    e. QTc > 480 msec based on Fridericia's corrected formula (QTcF)
    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening
    h. In France only, patients whose ejection fraction is < 45% should not enter the study.
3. Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
4. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
5. History of stroke or intracranial hemorrhage within 180 days before first dose of study drug
6. Severe or debilitating pulmonary disease
7. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
8. Active fungal, bacterial, and/or viral infection requiring systemic therapy
9. Known central nervous system involvement by lymphoma

10. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs
11. Known infection with HIV, or serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of hepatitis B core antibody (HBcAb), but absence of HBsAg, are eligible if HBV deoxyribonucleic acid (DNA) is undetectable (< 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation
    b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV ribonucleic acid (RNA) is undetectable (< 15 IU/mL)
12. Major surgery within 4 weeks of the first dose of study drug
13. Prior treatment with a BTK inhibitor
14. Last dose of prior therapy for MZL ≤ 21 days prior to first dose of study drug, with the following additional exclusion requirements:
    a. Treatment with monoclonal antibody-based therapy within 28 days of first dose of study drug
    b. Treatment with chimeric antigen receptor T-cell therapy within 180 days of first dose of study drug
    c. Treatment with any herbal medicine with anti-neoplastic intent within 28 days of first dose of study drug
    d. Allogenic hematopoietic stem cell transplantation within 12 months of first dose of study drug
15. Any chemotherapy or radiation treatment for non-MZL indications within 21 days of first dose of study drug
16. Toxicity from prior anti-cancer therapy that has not recovered to ≤ Grade 1 (except for alopecia, ANC, and platelet count; for ANC and platelet count, see Inclusion criterion 9)
17. Pregnant or lactating women
18. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
19. Ongoing alcohol or drug addiction
20. Hypersensitivity to zanubrutinib or any of the other ingredients in zanubrutinib
21. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
22. Received investigational drug within 30 days prior to first dose of zanubrutinib on this study or plans to receive another investigational drug during this study

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 8).

5.1. Visit Windows

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 4 days (ie, 4 days before or after the given day) for the first cycles and then ±7 days from Cycle 6 onward. After 48 weeks, the window for CT/MRI scans at subsequent visits is ± 14 days.

Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2. Informed Consent

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

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 35-day screening period. Consent must be obtained using the most current version of the form approved by the institutional review board (IRB) / independent ethics committee (IEC).

Repeating screening procedures or tests is allowed if the patient did not previously meet the inclusion and exclusion criteria, or if needed to have a documented result within the protocol-specified screening window.

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

5.3. Screening

All screening procedures must be performed within 35 days prior to first dose of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. The investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

5.3.1. Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology system to assign a unique patient number to a potential study participant. A patient number will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

5.3.2. Medical and Cancer History

Review all medical and cancer history after obtaining informed consent; including presence or absence of disease-related constitutional symptoms. Clinically significant medical history (eg, previous diagnoses, treatments, or surgeries) that do not pertain to the study indication, started before signing the informed consent, but considered relevant to the patient's study eligibility will be collected and captured in the electronic case report form (eCRF). "Clinically significant" is defined as any event, diagnosis, or laboratory value requiring treatment or 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.

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

5.3.3. Confirmation of Eligibility

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

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

5.3.4. Enrollment

After a patient has been approved by the medical monitor or designee to enroll in the study, study center personnel can enroll the patient in the Interactive Response Technology system to assign study drug. Study treatment should commence within 5 days after enrollment.

5.4. Zanubrutinib Dispensation

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

5.5. Safety Assessments

5.5.1. Cardiac Function

An assessment of left ventricular ejection fraction will be performed and documented at screening, and as medically indicated. An echocardiogram, multi-gated acquisition scan, or gated heart pool scan are all acceptable. In France only, patients whose ejection fraction is < 45% should not enter the study.

5.5.2. Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, heart rate, and body temperature), weight, and review for arrhythmia signs/symptoms (eg, shortness of breath, dizziness, or syncopal episodes) will be performed at each study visit during study treatment and at the Safety Follow-up Visit. Height (cm) is determined at screening only.

A complete physical examination includes an assessment of systems per standard of care at the study site and as clinically indicated by symptoms.

Assessment of vital signs and a focused physical examination on the first day of Cycle 1 may be skipped if performed within the last 7 days.

5.5.3. Eastern Cooperative Oncology Group Performance Status

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

5.5.4. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed locally in triplicate at screening for all patients and as clinically indicated at other timepoints.

5.5.5. Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 35 days before Cycle 1 Day 1, and on study thereafter.

5.5.6. Adverse Events Review

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

Collect non-serious AE information from the time of first dose of study drug through Safety Follow-up. Information on all SAEs (regardless of relatedness) will be collected from the time of signing of informed consent through screen failure or Safety Follow-up. The AE reporting period is defined in Section 8.4.1.

All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 8.1 and the definition of an SAE is provided in Section 8.2.1. Important additional requirements for reporting SAEs are explained in Section 8.

In addition, arrhythmia signs/symptoms will be reviewed at every cycle. This will involve the investigators asking patients for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness, or fainting), as part of the routine AE monitoring for each cycle.

5.6. Efficacy Assessments

Response will be assessed per the Lugano Classification for NHL (Cheson et al 2014) (Appendix 2). The primary endpoint is ORR based on the IRC. As secondary endpoints, investigators will also assess response locally according to Cheson et al 2014. The ORR according to Cheson et al 1999 will be assessed as an exploratory endpoint by IRC. Response parameters will include assessment of lymphadenopathy, organomegaly, and bone marrow examination. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 8).

Progressive disease must be confirmed by repeat imaging no sooner than 4 weeks from the first imaging that shows possible progression to rule out pseudo-progression. Patients may continue study treatment while they wait for the confirmatory imaging.

5.7. Tissue Collection with Central Diagnosis Confirmation

Archival tissue or fresh tissue from a screening biopsy (approximately 10 to 15 unstained formalin fixed paraffin embedded slides or tissue block) from an evaluable core or excisional biopsy will be collected at screening. Central review of the tissue will be performed to confirm diagnosis of MZL (central confirmation of MZL diagnosis not required for study entry). Patients without archival tissue must consent to a biopsy during screening to provide tissue for confirmation of diagnosis (approximately 10 to 15 unstained formalin fixed paraffin embedded slides or tissue block). If the diagnosis of MZL is not confirmed by central review, additional patients may be enrolled. It is requested but not required that patients with disease sites accessible have a biopsy during screening and submitted to BeiGene. All microscope slides or other tissue submitted become the property of BeiGene and could be used in support of research around the evaluation of potential disease markers using the DNA from the somatic tumor cells.

5.8. Pharmacokinetics

Blood will be collected to characterize the PK of zanubrutinib and/or its major metabolites. Blood samples (2 mL) for PK analysis will be collected into K_2EDTA collection tubes. Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the laboratory manual for this study.

PK samples will only be collected from sites that are able to adequately follow the sampling, handling, and processing procedures outlined in the laboratory manual.

On Cycle 1 Day 1 and Cycle 1 Day 28, patients will receive oral dosing of zanubrutinib at the clinic and dosing time and PK collection time will be collected on eCRF.

Intensive PK collection:

Blood will be collected from up to 15 patients participating at selected centers. PK samples will be collected from patients at the following timepoints.

- Cycle 1 Day 1: pre-dose (within 30 min prior to dose), and 0.5, 1, 2, 3, 4, 6 hours (± 15 min) post-dose
- Cycle 1 Day 28: pre-dose (within 30 min prior to dose), and 2 hours (± 15 min) post dosing

Sparse PK collection:

Sparse PK samples will be collected from all other patients. PK samples will be collected from patients at the following timepoints.

- Cycle 1 Day 1: pre-dose (within 30 min prior to dose), 2 hours (± 15 min) and between 4 to 6 hours (before patient discharge from the clinic) post dosing
- Cycle 1 Day 28: pre-dose (within 30 min prior to dose), and 2 hours (± 15 min) post dosing

5.9. Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of > 10% body weight within the previous 6 months) will be evaluated at screening and at 12, 24, 36, and 48 weeks, followed by every 24 weeks thereafter (Week 72, Week 96, and so on), and during Safety Follow-up and Long-term Follow-up Visits.

5.10. Computed Tomography

CT with contrast of neck, chest, abdomen, and pelvis will be performed at screening, at 12, 24, 36, and 48 weeks, followed by every 24 weeks thereafter (Week 72, Week 96, and on) until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. A CT scan does not need to be repeated if performed within 45 days before the Safety Follow-up Visit.

An MRI may be used in place of CT only for patients who cannot undergo CT due to contrast allergy. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is constant throughout a patient's course on study.

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

5.11. Positron Emission Tomography

A PET/CT scan or PET scan will be performed at screening. On a case-by-case basis, the window for the screening PET may be extended after discussion with the medical monitor for patients with IRC-confirmed non-avid disease. For patients with PET-avid disease at screening (as confirmed by IRC), PET scans will also be performed at 12, 24, 36, 48, and 72 weeks. For patients with PET-avid disease, an assessment of CR or PD must be confirmed by PET scan. All PET scans and PET/CT scans obtained during the study will be collected and reviewed by a central imaging vendor identified for this trial. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, central imaging vendor).

5.12. Bone Marrow Examination

Bone marrow biopsy and aspirate are required during the screening period. If patient has had a bone marrow biopsy as part of their standard care within 90 days of first dose of study drug, this biopsy may be used in place of a screening bone marrow biopsy and aspirate would not be required. If clinical and radiographical results demonstrate a potential CR on study treatment, a repeat bone marrow biopsy and aspirate are required for those with bone marrow involvement by MZL at screening. All bone marrow samples will be collected and reviewed both by the site local laboratory and by a pathologist from the central pathology laboratory.

5.13. Endoscopy

Endoscopy may be performed at screening for patients with gastrointestinal involvement of their MZL. Patients who had an endoscopy performed during the screening period which confirmed gastrointestinal involvement of MZL will require an endoscopy to confirm CR.

5.14. Patient-Reported Outcomes

Patient-reported outcomes will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedule of Assessments (Appendix 8) before study drug is administered and prior to performing any other procedures.

5.14.1. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The Euro Qol Group 1990; Herdman et al 2011). Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." A sample questionnaire is provided in Appendix 6 as an example only.

5.14.2. EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3000 studies worldwide. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties) (Fayers et al 2001). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in NHL patients. A sample questionnaire is provided in Appendix 7 as an example only.

5.15. Laboratory Assessments

Samples for protocol-specified complete blood count (CBC), chemistry, and coagulation profiles will be evaluated by a central laboratory. With BeiGene pre-approval, central lab collection may be substituted with local lab assessments. Additional laboratory assessments, including laboratory values required within a short time frame on dosing days to determine drug dosage, and unscheduled laboratory tests ordered by the investigator as necessary for patient monitoring, will be performed locally and entered into the eCRF as unscheduled labs, as applicable. Samples for serum immunoglobulins, serum protein electrophoresis, pregnancy testing, and HBV/HCV testing will be performed locally.

A detailed description of the procedures for sample collection, handling, storage, shipment of the laboratory samples, and all material such as test tubes and labels, is provided in the laboratory manual.

Chemistry, CBC, coagulation, serum immunoglobins, and serum protein electrophoresis will be performed at the timepoints specified in the Schedule of Assessments (Appendix 8) and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be done before the first dose of study drug.

5.15.1. Hematology

CBC with differential is required to be performed at screening, on Cycle 1 Day 1, then on Day 28 of each cycle indicated in the Schedule of Assessments (Appendix 8) during the treatment phase and during Safety Follow-up and Long-term Follow-up. CBC includes Hgb, hematocrit, platelet count, red blood cell count, white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil).

5.15.2. Chemistry

Serum chemistry is required to be performed at screening, on Cycle 1 Day 1, then on Day 28 of each cycle indicated in the Schedule of Assessments (Appendix 8) during the treatment phase and during Safety Follow-up and Long-term Follow-up, and includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate or phosphorous, magnesium, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase.

5.15.3. Serum Protein Electrophoresis

Serum protein electrophoresis will be measured at screening, then every 6 cycles thereafter until PD, and as clinically indicated. Patients with a monoclonal spike (M spike or paraprotein) on serum protein electrophoresis at screening should have *MYD88* mutational analysis conducted to rule out a diagnosis of Waldenström's macroglobulinemia. Patients positive for *MYD88* mutation will be excluded only if it is determined that the patient has Waldenström's macroglobulinemia.

5.15.4. Serum Immunoglobulins

Quantitative serum immunoglobulins (immunoglobin G, immunoglobin M, immunoglobin A) will be measured at screening, Cycle 3, 6, 9, 12, then every 6 cycles thereafter during and after the treatment phase.

5.15.5. Coagulation

The coagulation profile includes prothrombin time, which may also be reported as international normalized ratio and activated partial thromboplastin time. The coagulation profile will be performed at screening only, and as clinically indicated.

5.15.6. Hepatitis B and C testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb) as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

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

If, during monthly monitoring of HBV DNA by PCR, the value is between 20 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drug should be stopped and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped and antiviral therapy initiated or continued. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by physicians with expertise in managing hepatitis C.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation. Table 1 describes how the results for HBV and HCV testing at screening relate to study eligibility.

Table 1: Active Hepatitis B or Hepatitis C Infection (Detected Positive by Polymerase Chain Reaction)

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) ***HBV DNA "Not detected"*** *Perform monthly monitoring of HBV DNA* *(if antiviral treatment is ongoing, perform monitoring every 90 days)*	**HBsAg (-) *and* HBcAb (+)** ***HBV DNA detected***
HCV	**Antibody (-) *or* Antibody (+)** ***HCV RNA "Not detected"*** *Perform monthly monitoring of HCV RNA*	**Antibody (+)** ***HCV RNA Detected***

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus: deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid.

5.15.7. Pregnancy Test

A serum pregnancy test will be performed at screening within 7 days of enrollment and End of Treatment in women of childbearing potential (including those who have had a tubal ligation). Any female patient 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, then on Day 28 of every cycle. Pregnancy tests must be continued every 4 weeks for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

5.16. Unscheduled Visits

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

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

5.17. End of Treatment Period

The treatment period starts with the first day of assigned study treatment and continues until the last administered dose of zanubrutinib.

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

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

Patients may voluntarily withdraw consent from treatment at any time.

5.18. Safety Follow-up

All patients who permanently discontinue study drug will have a Safety Follow-up Visit approximately 30 days after the last dose of study drug to collect AEs, including AEs that may have occurred or been ongoing after the patient discontinued study treatment. The investigator or his/her designee will also continue to collect information on new anti-cancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information. Refer to the Schedule of Assessments (Appendix 8) for the assessments to be performed at the Safety Follow-up Visit.

5.19. Long-term Follow-up

All patients who discontinue study drug treatment will remain in the study, complete Safety Follow-up, and subsequently commence Long-term Follow-up, which includes monitoring survival status and subsequent therapies for MZL, and chemistry and hematology assessments. Patients who discontinue study drug due to reasons other than disease progression will remain on study and should be followed with CT/MRI/PET every 12 weeks until Week 48, then every 24 weeks (± 14 days) thereafter until documented disease progression, new anticancer therapy, death, or study closure, whichever occurs first.

For patients who permanently discontinue study drug treatment before radiographic progression is documented, tumor assessments (including radiographic imaging) will continue until radiographic progression is identified and confirmed by the investigator. Imaging assessments should occur according to the Schedule of Assessments (Appendix 8).

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

5.20. End of Study

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

- Withdrawal by the patient
- Lost to follow-up
- Study termination by sponsor
- Physician decision
- Other

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

The end of the study is defined as the last visit (the 30 days safety follow-up contact) of the last patient undergoing study treatment on this protocol or when the last patient undergoing study treatment has been transitioned onto an extension study.

5.21. Lost to Follow-up

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

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

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

6. STUDY TREATMENT

6.1. Study Treatment Preparation and Dispensation

6.1.1. Packaging and Labeling

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

6.1.2. Handling and Storage

The Interactive Response Technology 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 acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. The study drugs must be kept at the temperature condition as specified on the labels.

Zanubrutinib bottles must be stored at the temperature specified on the label.

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

6.1.3. Compliance and Accountability

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

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

6.1.4. Disposal and Destruction

After completion of the study, and following final drug inventory reconciliation by the monitor, the study site will destroy or return all unused study drug supplies. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.2. Dosage and Administration

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at approximately the same time each day of dosing. Patients will be asked to complete a patient diary that records dates and times of dosing between clinic visits. Patients will be requested to bring their diaries, unused medication, and all empty bottles, to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

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

If a dose of the study drug is not taken at the scheduled time, the patient should skip the study drug if the time to next dose is less than 8 hours and return to normal dosing with next dose. If a patient vomits after taking the zanubrutinib capsules, that dose should not be repeated.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Signs and symptoms of an overdose that meet any SAE criterion must be reported as described in Section 8.5.1. There is no specific antidote for zanubrutinib overdose. In an event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

6.3.1. Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment with zanubrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding.

6.4. Dose Interruption and Modification

The guidelines below should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.4.1) and non-hematologic (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events; laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) (Section 6.4.2) toxicities.

Table 2: Zanubrutinib Dose Reduction Levels

Toxicity Occurrence	Dose Level	Zanubrutinib Dose
First	0 = starting dose	Restart at 160 mg twice daily
Second	-1 dose level	Restart at 80 mg twice daily
Third	-2 dose level	Restart at 80 mg once daily
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

Zanubrutinib may be restarted upon resolution of toxicity and per investigator discretion if held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the medical monitor.

6.4.1. Dose Reduction for Hematologic Toxicity

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

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

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

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

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

6.4.2. Dose Reduction for Non-hematologic Toxicity

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

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

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

Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.15.6.

6.5. Warnings and Precautions

For information on warnings and precautions for zanubrutinib, refer to the Zanubrutinib Investigator's Brochure. 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 disease and treatment-related factors. In patients with a high risk for opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PJP), prophylaxis should be considered as per institutional standards.

Tumor lysis syndrome has been infrequently reported with zanubrutinib treatment, particularly in patients who were treated for chronic lymphocytic leukemia. Patients with high tumor burden should be assessed, monitored closely, and treated per institutional guidelines. Prophylactic measures including allopurinol may be instituted per institutional standards.

7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

Medications taken within 4 weeks before first dose and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, will be recorded on the eCRF and in the patient's source documents.

All prior therapies for marginal zone lymphoma, including immunochemotherapy, chemotherapy, transplant, targeted therapy, radiation therapy, etc. will be recorded on the eCRF with the dates of administration.

Per the study eligibility criteria, patients who received certain prior medications and therapies for marginal zone lymphoma (including allogeneic hematopoietic stem cell transplantation within 12 months of study enrollment and prior exposure to a BTK inhibitor) are excluded from study participation.

7.2. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the eCRF.

7.2.1. Permitted Medications

The following treatments are allowed:

- Blood product transfusion and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-NHL indication(s)
- Patients should not receive treatment with systemic corticosteroid other than intermittently to control or prevent infusion reactions or for short durations (< 2 weeks) to treat non-NHL-related condition(s) (eg, to treat a flare of chronic obstructive pulmonary disease). Chronic systemic corticosteroid use is not permitted, except for adrenal replacement, and requires consultation with the medical monitor.
- Therapy to reduce symptoms per standard of care and institutional guidelines

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 disease and treatment-related factors. In patients with a high risk for opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PJP), prophylaxis should be considered as per institutional standards.

7.2.2. Prohibited Medications

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

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

7.3.1. Effects of CYP-Inhibiting/Inducing Drugs on Exposure of Zanubrutinib

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 4 for a list of these medications), grapefruit juice, and Seville oranges should be done with caution, as they may affect the metabolism of zanubrutinib (Section 1.3.2.2). 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 guidance in Table 3. 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.

In the event of suspected drug-drug interactions (eg, when a strong or moderate CYP3A inducer must be used for controlling an infection), close monitoring of zanubrutinib drug concentrations may be needed by taking additional unscheduled PK samples.

7.3.2. Effects of Zanubrutinib on Exposure of Other Concomitant Medications

A clinical drug-drug interaction study (Study BGB-3111-108) indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.3.2.2). Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs.

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 4.1).

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}. 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.

Table 3: Dose Modification for Zanubrutinib when Coadministered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Coadministered 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, 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.

CYP3A	Coadministered drug	Recommended use
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin, rifabutin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

8. SAFETY MONITORING AND REPORTING

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

8.1. Adverse Events

8.1.1. Definitions and Reporting

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

Examples of an AE include:

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

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) related 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 these instances, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

If a patient initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

8.1.1.1. 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 will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living

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

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

8.1.1.2. Assessment of Causality

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

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

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE 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 in light of follow-up information, amending the SAE report accordingly.

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

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

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

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.1.

8.1.2. Laboratory Test Abnormalities

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

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

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C, see Section 5.15.6.

8.1.3. Lack of Efficacy

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

8.2. Serious Adverse Events

8.2.1. Definitions

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

- Results in death
- Is life-threatening

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

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

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

The following are NOT considered SAEs:

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

8.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure.

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

8.4.1. Adverse Event Reporting Period

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

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

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

8.4.2. Eliciting Adverse Events

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

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

8.5. Specific Instructions for Recording Adverse Events and Serious Adverse Events

8.5.1. Diagnosis versus Signs and Symptoms

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

8.5.2. Persistent or Recurring Adverse Events

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

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

8.5.3. Disease Progression

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

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

8.5.4. Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, “death”, “death of unknow cause”, or “death unexplained”.

8.6. Prompt Reporting of Serious Adverse Events

8.6.1. Time Frames for Submitting Serious Adverse Events

SAEs will be reported promptly to the sponsor or designee as described in Table 4 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 4: Time Frame for Reporting SAEs to the Sponsor or Designee

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

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

8.6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 8.6.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated time frames.

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

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

The sponsor will provide contact information for SAE receipt.

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

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

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

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

8.7. Pregnancy Reporting

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

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

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

8.8. Post-Study Adverse Event

A post-study AE or SAE is defined as any AE that occurs after the AE/SAE reporting period, defined in Section 8.4.1.

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

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

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the BGB-3111 Investigator's Brochure.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized according to sponsor-agreed reporting standards.

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

9.1. Study Endpoints

9.1.1. Primary Endpoint

The primary endpoint is ORR (CR + PR) in accordance with the Lugano Classification (Cheson et al 2014) and determined by the IRC.

9.1.2. Secondary Endpoints

The secondary endpoints are:

- ORR (CR + PR) in accordance with the Lugano Classification (Cheson et al 2014) determined by investigator assessment
- ORR (CR + PR) in accordance with the Lugano Classification (Cheson et al 2014) using PET assessment data for patients with FDG (F-fluoro-2-deoxy-d-glucose)–avid disease determined by IRC
- PFS in accordance with the Lugano Classification (Cheson et al 2014) determined by IRC and by investigator assessment
- OS
- DOR in accordance with the Lugano Classification (Cheson et al 2014) determined by IRC and by investigator assessment
- TTR in accordance with the Lugano Classification (Cheson et al 2014) determined by IRC and by investigator assessment
- Time to treatment failure
- Time to next line of therapy for MZL
- PROs measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaire
- Safety parameters including AEs, SAEs, laboratory tests, physical exams, and vital signs
- PK parameters such as apparent clearance of the drug from plasma (CL/F) and $AUC_{0\text{-}12}$

9.1.3. Exploratory Endpoints

- ORR (CR + complete remission unconfirmed [CRu] +PR) in accordance with Cheson et al 1999 as determined by IRC

9.2. Statistical Analysis

9.2.1. Analysis Sets

The safety analysis set includes all patients who were enrolled and received any dose of zanubrutinib. This will be the set of primary interest for safety analyses. The efficacy analysis set consists of all patients in the safety analysis set with confirmed MZL. This set will be the primary analysis set for efficacy analyses. The PK analysis set includes all patients who have at least one PK sample collected (have at least one post-dose PK concentration) according to the protocol and laboratory manual.

9.2.2. Patient Disposition

The number of patients enrolled, treated, and discontinued from study drug will be summarized. The primary reason for study drug discontinuation will be summarized according to the categories recorded in the eCRF. The end of study status (alive, death, withdrew consent, or lost to follow-up) at the data cut-off date will be summarized using the data from the eCRF.

9.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized. Continuous variables include age, height, weight, vital signs; categorical variables include sex, age group, race, ethnicity, ECOG performance status, and geographic region.

9.2.4. Disease History

The number (percentage) of patients reporting a history of disease and disease characteristic will be summarized. Disease characteristics include time since first diagnosis of MZL to study entry, time from most recent relapse or refractory to study entry, disease subtype, sites of disease, evidence of FDG-avid disease, and involvement in bone marrow.

9.2.5. Prior and Concomitant Therapy

Prior and concomitant medications will be assigned a preferred name using the World Health Organization Drug Dictionary drug codes. Prior and concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical class indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by preferred name and therapeutic class. Prior medications will be defined as medications that 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 patient's last dose or initiation of a new anti-cancer therapy.

Prior anti-cancer therapy will be summarized, which includes number of patients with prior systemic therapy, number of lines of prior therapies, number of prior regimens, number of prior regimens with CD20-directed therapies, time from end of last regimen to study entry, time from end of progression on last regimen to study entry, reason last regimen ended, best overall response to last regimen, number of patients with prior radiotherapy, and time from the end of last radiotherapy to study entry.

9.2.6. Medical History

Medical history will be mapped to a system organ class (SOC) and a preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) of the version currently in effect with the sponsor at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by SOC and PT.

9.2.7. Efficacy Analysis

9.2.7.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is ORR according to the Lugano Classification (Cheson et al 2014) (Appendix 2) as assessed by IRC. ORR is defined as the proportion of patients achieving a best overall response of CR or PR. A two-sided Clopper-Pearson 95% CI for ORR will be calculated.

Patients with no postbaseline response assessment will be considered non-responders for the purposes of analysis. The proportion for each response category (CR, PR, SD, and PD) will be presented. The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient received the first dose of study drug.

9.2.7.2. Secondary Efficacy Endpoint Analyses

ORR based on the investigator assessment and ORR using PET assessment by IRC will be summarized using same statistical methods employed in the primary efficacy analysis.

PFS is defined as time from study treatment start to PD or death, whichever is earlier. The Kaplan-Meier method will be used to summarize PFS and corresponding quartiles (including the median). Two-sided 95% CIs for quartiles will be provided. The PFS probability at selected timepoints (eg, 23 weeks) will be estimated along with the corresponding 95% CI. The PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018). The analysis methods for PFS per IRC and per investigator will be the same.

OS is defined as time from study treatment start to death due to any cause. Duration of response is defined as time from first response (PR or better) to PD or death, whichever is earlier.

The distribution of DOR and OS will be summarized by the Kaplan-Meier method. The analysis methods for DOR per IRC and, per investigator will be the same.

TTR is defined as time from study treatment start to first assessment of a response of PR or better and will be summarized. The analysis methods for TTR per IRC and per investigator will be the same.

TTF is defined as time from study treatment start to discontinuation of study drug due to any reason. TTF will be censored at the data cutoff for the patients who didn't discontinue study treatment. TTF will be summarized by the Kaplan-Meier method.

Time to next therapy is defined as time from study treatment start to start of first subsequent therapy for MZL. Time to next therapy for MZL will be summarized by the Kaplan-Meier method.

PROs (QLQ-C30, EQ-5D-5L) at each assessment timepoint and changes from baseline will be summarized.

9.2.7.3. Exploratory Efficacy Analyses

ORR (CR + CRu + PR) in accordance with Cheson et al 1999 as determined by IRC will be summarized using same statistical methods employed in the primary efficacy analysis.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (CBC, serum chemistry, coagulation), vital signs, physical exams and ECG findings will also be used in assessing safety.

9.3.1. Extent of Exposure

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

The number (and percentage) of patients with dose reductions and dose interruption will be summarized with the respective reasons. The cycles in which dose reduction/interruption occurred will be summarized using descriptive statistics.

9.3.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized PT and SOC using MedDRA.

A TEAE is defined as an AE that had an onset date on or after the first dose of study drug and up to 30 days following study drug discontinuation, or the start of new anti-cancer 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 patient data listings.

TEAEs of any grade, SAEs, TEAEs grade 3 or above, TEAEs leading to treatment discontinuation, dose reduction, or dose interruption, TEAEs leading to death, and treatment-related AEs will be summarized. TEAEs will also be summarized by SOC, PT, and worst grade. A patient will be counted only once by the highest severity grade according to NCI-CTCAE v4.03 within a SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

Incidence and time to selected TEAEs of special interest such as severe hemorrhage (defined as ≥ Grade 3 hemorrhage of any site or central nervous system hemorrhage of any grade) and atrial fibrillation (both new onset and exacerbation of existing atrial fibrillation) will also be summarized.

The number of deaths and the cause of death will also be summarized.

9.3.3. Laboratory Analyses

Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Laboratory data (actual value and change from baseline) will be summarized by visit.

Laboratory parameters that are graded in NCI-CTCAE (v.4.03) will be summarized by CTCAE grade. Shift tables will be used to assess the change of each laboratory parameter from its toxicity grade at baseline to the worst post-baseline toxicity grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, phosphorus, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

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

9.3.5. Electrocardiogram

Descriptive statistics for electrocardiogram (ECG) parameters by visit and change from baseline (if post-baseline ECG parameters are measured) will be presented.

9.3.6. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarized by visit and change from baseline (if post-baseline ECOG is measured) will be presented.

9.4. Pharmacokinetic Analyses

The analysis set for patients with PK samples will contain all patients who had at least one PK sample collected according to the protocol and laboratory manual. Actual collection times will be used in the final analysis and reporting.

For intensive PK profile, pharmacokinetic parameters such as C_{max}, AUC, and half-life will be derived using the standard non-compartmental method. For intensive PK data (Week 1 Day 1), individual and mean plasma zanubrutinib concentration-time data will be summarized and displayed in both tabular and graphical form.

In addition, all PK data (intensive and sparse PK) from this study, along with data from other zanubrutinib trials will be included in the population PK and exposure-response analysis to understand potential covariates impacting PK of zanubrutinib and to assess relationships between exposure (eg, C_{max} and AUC) and efficacy and safety endpoints. These analyses will be reported separately.

9.5. Sample Size Consideration

Assuming a null hypothesized ORR of 30%, a sample size of 65 patients will provide 82% power for the alternative ORR of 48%, at a 1-sided alpha level of 0.025 and using the exact binomial test. The alternative ORR is based on the observed ORR for the ibrutinib study in R/R MZL (Noy et al 2017). For an observed ORR of 48% (31/65), the 95% exact binomial confidence interval is (35%, 60%).

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Review Committee

The sponsor will contract with an IRC facility to provide an independent review of imaging and clinical data necessary to assess tumor response in this study. This will be conducted by qualified, board-certified radiologists and hematologists assigned to this study. An IRC charter will describe the independent review and define the processes, roles, and responsibilities of the sponsor, the sites, the IRC facility, and the reviewers.

10.2. Steering Committee

This study will be overseen by a Steering Committee consisting of experts in lymphoma and members of the sponsor's staff. The Steering Committee plays a central role in the design of the study, oversees the conduct of the study, and agrees on a plan for communication of the results.

10.3. Safety Monitoring Committee

A Safety Monitoring Committee consisting of experts in lymphoma, clinical trial safety monitoring, and statistics will evaluate data on a periodic basis for this study. Approximately every 6 months, the Monitoring Committee will review all available safety data. A separate charter will outline the details for the composition and responsibility of the Safety Monitoring Committee.

10.4. Provision of Study Results and Information to Investigators

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

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

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

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

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

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

11.2.2. Ethical Conduct of the Study and Ethics Approval

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

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

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

11.2.3. Informed Consent

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

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

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.6.3, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IRB/IEC, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IRB/IEC. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

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

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

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

11.2.6. Data Collection

Data required by the protocol will be entered into an EDC system.

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

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

11.2.7. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies and completeness.

During the course of the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

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

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

11.2.8. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these

procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

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

11.2.9. 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.

11.2.10. Protocol Adherence

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

11.2.11. Financial Disclosure

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

11.2.12. Protocol Modifications

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

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

11.3. Study Report and Publications

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2013).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsors 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 Sponsor to allow for patent filings in advance of the publication/presentation.

11.4. Study and Study Center Closure

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

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

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance with this protocol, Good Clinical Practice, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action 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 IRB/IEC promptly and provide the reason for the suspension or termination.

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

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

11.5. Records Retention and Study Files

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

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

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

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

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

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

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

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

11.6. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 11.3.

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

11.7. Joint Investigator/Sponsor Responsibilities

11.7.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

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

11.7.2. Access to Information for Auditing or Inspections

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

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APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma

PROTOCOL NO: BGB-3111-214

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

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 BeiGene or its designee.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2. THE LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA (CHESON ET AL, 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3* with or without a residual mass on 5PS[†] It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi • No extra-lymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement[♦]	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology (if BMA involved at screening), if indeterminate, IHC negative
Partial	Partial metabolic response:	Partial remission (all of the following):
Lymph nodes and extra-lymphatic sites	Score 4 or 5[†] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When no longer visible, 0 x 0 mm • For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following:

Individual target nodes/nodal masses	Score 4 or 5† with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with:
		• LDi > 1.5 cm and
		• Increase by ⩾ 50% from PPD nadir and
		• An increase in LDi or SDi from nadir
		  ○ 0.5 cm for lesions ⩽ 2 cm
		  ○ 1.0 cm for lesions > 2 cm

Non-measured lesions	None	New lesions or clear progression of pre-existing non-measured lesions: • Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	
Organ enlargement	Not applicable	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). • If no prior splenomegaly, must increase by at least 2 cm from baseline
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; BMA, bone marrow assessment; CT, computed tomography; FDG, F-fluoro-2-deoxy-d-glucose; IHC, immunohistochemistry; LDi, longest diameter; PET, positron emission tomography; PPD, percent platelet decrease; SDi, shortest diameter; SPD, sum of the products of diameters.
Source: Cheson et al 2014

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

♦Splenomegaly defined as vertical spleen length > 13 cm.

†PET 5-point scale (Deauville Criteria):

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

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

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, or lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation.

Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (eg, gastrointestinal tract, liver, or bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors.

APPENDIX 3. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20 to 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA, New York Heart Association.

APPENDIX 4. CYP3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors
Antibiotic: clarithromycin, telithromycin, troleandomycin
Antifungal: itraconazole, ketoconazole, posaconazole, voriconazole
Antiviral: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, nefazodone
Protease inhibitor: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Food products: grapefruit juice (*Citrus paradisi* juice)
Herbal medications: Schisandra sphenanthera
Other: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers
Abbreviations: CYP3A: cytochrome P450, family 3, subfamily A.
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.
For a more complete list, please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ or to Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. http://medicine.iupui.edu/flockhart/table.htm

APPENDIX 5. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

APPENDIX 6. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

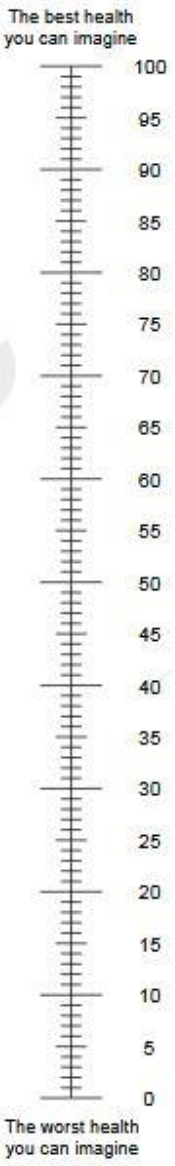
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

APPENDIX 7. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

APPENDIX 8. SCHEDULE OF ASSESSMENTS

Study Period or Visit	Screening	Treatment (1 cycle = 28 days)					Continue Assessments Until Disease Progression	Post-Treatment Follow-Up	
Cycle	–	**1**	**1 and 2**	**3**	**4 and 4**	**Cycles 6, 9, 12, 15, 18, 21, 24, … (every 3 cycles)**		**Safety Follow-up[a]**	**Long-Term Follow-up[u]**
Cycle Day	**-35 to -1**	**1**	**28 (Study Days 28 & 56)**	**28 (Study Day 84)**	**28 (Study Days 112 & 140)**	**28 (Study Days 168, 252, 336, 420, etc.)**		**30 ± 7 days after EOT**	**Every 24 weeks**
Window (Days)	–	–	**± 4**	**± 4**	**± 4**	**± 7**			**± 14 days**
Informed consent	X								
Medical & cancer history	X								
Eligibility authorization packet	X								
Zanubrutinib dispensing/accountability		X	X	X	X	X			
Tissue collection (archival or screening)[b]	X								
Safety Assessments									
Cardiac function test[c]	X								
Vital signs (temperature, BP, heart rate)[d]	X	X	X	X	X	X		X	
Physical examination[d]	X	X	X	X	X	X		X	
ECOG performance status	X	X	X	X	X	X		X	
12-lead ECG (local read)[e]	X								
Concomitant medications review	X	X	X	X	X	X		X	X
AE review[f]		X	X	X	X	X		X	

Study Period or Visit	Screening	Treatment (1 cycle = 28 days)					Continue Assessments Until Disease Progression	Post-Treatment Follow-Up	
Cycle	–	1	1 and 2	3	4 and 5	Cycles 6, 9, 12, 15, 18, 21, 24, ….. (every 3 cycles)		Safety Follow-up[a]	Long-Term Follow-up[u]
Cycle Day	-35 to -1	1	28 (Study Days 28 & 56)	28 (Study Day 84)	28 (Study Days 112 & 140)	28 (Study Days 168, 252, 336, 420, etc.)		30 ± 7 days after EOT	Every 24 weeks
Window (Days)	–	–	± 4	± 4	± 4	± 7			± 14 days
Efficacy Assessments									
Disease-related constitutional symptoms[g]	X			X		X		X	X
CT with contrast[h, i]	X			X		X[h]		X[i]	X
PET scan[j]	X			X		X[j]			X[j]
Bone marrow examination[k]	X	At time of CR[k]							
Endoscopy[l]	optional	At time of CR if performed at screening							
PRO questionnaires[m]		X		X		X[m]		X	X
Laboratory Assessments									
Pharmacokinetics[n]		X	X (Cycle 1 Day 28 only)						
Hematology, chemistry[o, p]	X	X	X	X	X	X [o, p]		X	X [o, p]
Serum immunoglobulins[q]	X			X		X[q]			
Serum protein electrophoresis[r]	X					X[r]			
Coagulation	X								
Hepatitis B & C testing[s]	X								
Pregnancy test (if applicable)[t]	X	X	X	X	X	Every cycle		X	X[t]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BTK, Bruton tyrosine kinase; CR, complete response; CRi, complete remission with incomplete bone marrow recovery; CT, computed tomography; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EOT, end

of treatment; EQ 5D-5L, 5-level EQ-5D version; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus; Hct, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; hrs, hours; LDH, lactate dehydrogenase; LTFU, long-term follow-up; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD, progressive disease; PET, positron emission tomography; PRO, patient-reported outcome; RBC, red blood cell; RNA, ribonucleic acid; SAE, serious adverse event; WBC, white blood cell.

a. Approximately 30 days (± 7 days) after permanent treatment discontinuation.
b. Submission of archival tissue or fresh tumor tissue sample from an evaluable core or excisional biopsy (approximately 10-15 unstained formalin fixed paraffin embedded slides or tumor block) for central confirmation of diagnosis is mandatory. Central confirmation of MZL diagnosis not required for study entry. It is requested but not required that patients with disease sites accessible have a biopsy during screening and submitted to BeiGene. All microscope slides or other tissue submitted become the property of BeiGene and could be used for research around the evaluation of potential disease markers using the DNA from the somatic tumor cells.
c. An assessment of left ventricular ejection fraction will be performed and documented at screening, and as medically indicated. Echocardiogram, multi-gated acquisition scan, or gated heart pool scan are all acceptable. In France only, patients whose ejection fraction is < 45% should not enter the study.
d. A complete physical examination includes an assessment of systems per standard of care at the study site and as clinically indicated by symptoms. Vital signs include sitting blood pressure, heart rate, body temperature, and body weight. Height (cm) is determined at screening only. Assessment of vital signs and a focused physical examination on the first day of Cycle 1 may be skipped if performed within the last 7 days.
e. A 12-lead ECG will be performed locally in triplicate at screening for all patients, and as clinically indicated at other timepoints.
f. Collect nonserious AE information from the time of first dose of study drug through safety follow-up. Collect SAE information from the time of signed informed consent through screen failure or safety follow-up. In addition, arrhythmia signs/symptoms will be reviewed at every cycle. This will involve the investigators asking patients for signs and symptoms of ventricular dysfunction (eg, shortness of breath, dizziness, or fainting), as part of the routine AE monitoring for each cycle.
g. Disease related constitutional symptoms will be evaluated at screening, at 12, 24, 36, and 48 weeks - followed by every 24 weeks thereafter (Week 72, Week 96, and so on), and during Safety Follow-up and Long-term Follow-up.
h. CT scan with contrast of neck, chest, abdomen, and pelvis to be performed at screening, at 12, 24, 36, and 48 weeks - followed by every 24 weeks thereafter (Week 72, Week 96, and so on) until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Copies of all scans will be sent to IRC for response assessment. MRI may be substituted for patients with serious contrast allergy, but it should be used consistently. After 48 weeks, the window for CT/MRI scans for subsequent visits is ± 14 days.
i. A CT scan does not need to be repeated if performed within 45 days before the Safety Follow-up Visit.
j. PET scan will be performed at screening for all patients. On a case-by-case basis, the window for the screening PET may be extended after discussion with the medical monitor for patients with IRC-confirmed non-avid disease. Patients with PET-avid disease at screening, as confirmed by the IRC, will have PET scan repeated at 12, 24, 36, 48, and 72 weeks. For patients with PET-avid disease, an assessment of CR or PD must be confirmed by PET scan.
k. Bone marrow biopsy and aspirate are required during the screening period. If patient has had a bone marrow biopsy as part of their standard care within 90 days of first dose of study drug, this biopsy may be used in place of a screening bone marrow biopsy and aspirate is not required. Bone marrow biopsy and aspirate are also required if clinical and laboratory results demonstrate a potential CR to confirm CR for those with positive bone marrow involvement by MZL at screening. All bone marrow samples will be collected and reviewed both by the site local laboratory and by a pathologist from the central pathology laboratory.
l. Endoscopy may be performed at screening for patients with gastrointestinal involvement of their MZL. Patients who had an endoscopy performed during the screening period which confirmed gastrointestinal involvement of MZL will require an endoscopy to confirm CR.

m. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug, and before performing any other procedures. The questionnaires are to be completed on Cycle 1 Day 1, end of Cycle 3, then every 12 weeks for 12 months, followed by every 24 weeks thereafter. Patient-reported outcomes will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation.

n. Intensive PK will be collected from up to 15 patients at selected sites on Cycle 1 Day 1 (pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs [±15 min] post-dose) and on Cycle 1 Day 28 (pre-dose and 2 hrs [±15 min] post-dose). Sparse PK will be collected from all other patients at all other sites on Cycle 1 Day 1 (pre-dose, 2 hrs [±15 min] and between 4 to 6 hours post-dose) and on Cycle 1 Day 28 (pre-dose and 2 hrs [±15 min]).

o. Complete blood count includes Hgb, Hct, platelet count, RBC count, WBC count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil). Complete blood count and differential will be evaluated by a central laboratory, and is required at screening, on Cycle 1 Day 1, then on Day 28 from cycles 2 to 5. From cycle 6, hematology assessments are to continue every 12 weeks (ie, every 3 cycles) during the treatment period. The hematology assessments are to continue during LTFU every 24 weeks.

p. Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, total bilirubin, total protein, albumin, ALT, AST, LDH, and alkaline phosphatase. Serum chemistry will be evaluated by a central laboratory, and is required at screening, on Cycle 1 Day 1, then on Day 28 from Cycles 2 to 5. From Cycle 6, serum chemistry assessments are to continue every 12 weeks (ie, every 3 cycles) during the treatment period. The serum chemistry assessments are to continue during LTFU every 24 weeks.

q. Quantitative serum immunoglobulins (IgG, IgM, IgA) will be measured at screening, Cycle 3, 6, 9, 12, then every 6 cycles thereafter during and after the treatment phase.

r. Serum protein electrophoresis will be measured at screening, then every 6 cycles thereafter until PD, and as clinically indicated. Patients with a monoclonal spike (M spike or paraprotein) on serum protein electrophoresis at screening should have MYD88 mutational analysis conducted to rule out a diagnosis of Waldenström's macroglobulinemia. Patients positive for MYD88 mutation will be excluded only if it is determined that the patient has Waldenström's macroglobulinemia.

s. Viral hepatitis B serology includes HBsAg, HBcAb, HBsAb. Patients who are HBcAb positive and HBsAg negative and negative for HBV DNA by PCR at screening will undergo viral load measurement (HBV DNA by PCR) monthly, unless they are being treated prophylactically with antivirals in which case, they must be tested every 90 days. Viral hepatitis C serology includes HCV antibody. Patients who are HCV antibody positive at screening, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly.

t. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening (within 7 days of enrollment) and at end of treatment. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed on Cycle 1 Day 1, then on Day 28 of every cycle. Pregnancy tests must be continued every 4 weeks for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

u. For patients who permanently discontinue study drug treatment before radiographic progression, tumor assessments (including radiographic imaging) will continue on the same schedule as outlined for imaging schedule until radiographic progression is confirmed. Imaging assessments should occur according to the Schedule of Assessments: every 12 weeks until Week 48, then every 24 weeks thereafter.