BeiGene

BGB-3111-205 (NCT03206918)

A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Document Type: Clinical Study Protocol

Document Date: Oct 25, 2017

Clinical Study Protocol

Protocol Title:	**A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)**
Protocol Number:	**BGB-3111-205**
Date of Protocol:	**25 October 2017, Version 2.0**
Study Phase:	**2**
Sponsor:	**BeiGene (Beijing) Co., Ltd** **No. 30 Science Park Road** **Zhong-Guan-Cun Life Science Park** **Changping district, Beijing 102206** **China**
Sponsor Medical Monitor:	**Meng Ji, MD** **BeiGene (Beijing) Co., Ltd**

SIGNATURES

PROTOCOL TITLE: A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

PROTOCOL NO: BGB-311-205

DATE OF PROTOCOL: 25 October 2017

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PROTOCOL AMENDMENT (VERSION 2.0)

Protocol BGB-3111-205 is amended primarily for the following reasons:

1. To clarify that the primary and secondary efficacy objectives and endpoints will be assessed by an Independent Review Committee (IRC), and to add ORR by investigator as a secondary objective and endpoint.
2. To clarify and refine Inclusion and Exclusion criteria
3. To update the BGB-3111 clinical information
4. To update safety monitoring and reporting information
5. To clarify BGB-3111 dose reductions
6. To clarify QT-prolonging medications and CYP-inhibiting/inducing drugs
7. To clarify the response criteria for chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL)

Throughout are administrative updates, editorial changes, and/or style and formatting revisions made with the purpose of improving clarity and consistency throughout the document.

Major changes to the protocol are as follows:

Synopsis and Section 6.6: Revised Prohibited Concomitant Therapy and Permitted Medications language describing allowed corticosteroids dosage to align with Exclusion criterion #3.

Synopsis, Section 2.1, Section 2.2, Section 3.1, Section 3.2, Section 7.3, Section 10.1, and Section 10.2.5: Clarified that the primary and secondary efficacy objectives and endpoints will be assessed by an IRC.

Synopsis, Section 2.2, Section 3.2, Section 10.1.2, Section 10.2.5.2: Added ORR by investigator as a secondary objective and endpoint.

Synopsis and Section 5.1:

- Inclusion criteria #1, #6, #7, #11, #13, and #14 were clarified.
- Inclusion criterion #18 (Echocardiogram [ECHO] must demonstrate left ventricular ejection fraction [LVEF] ≥50%) was added.

Synopsis and Section 5.2:

- Exclusion criteria #3, #7, #8, #10, #11, #14, and #16 were clarified.
- Exclusion criterion #17 (Has received allogenic hematopoietic stem cell transplantation prior to enrollment) was added

Synopsis, Section 3.2, Section 10.1.2, and Section 10.3.2: Removed secondary endpoint of incidence of adverse events of special interest (AESI), and AESI from the protocol as there are no AESIs for BGB-3111 according to current safety data.

Synopsis, Section 4.1, Section 6.7.1, and Section 9.5: Revised text to clarify that if a patient discontinues due to an AE, they are still followed for disease progression, regardless of if new anticancer therapy is started.

Synopsis, Section 5.2 (Exclusion criterion #11) and Section 7.4.4.9: Revised text to provide additional clarification of Hepatitis B and C restrictions and testing

Synopsis and Section 6.5: Clarified when BGB-3111 dosing should be held and that BGB-3111 can be stopped earlier if medically indicated.

Synopsis and Section 6.6: Clarified permitted and prohibited concomitant medications and therapies, QT-prolonging medications, and CYP-inhibiting/inducing drugs.

Synopsis and Section 9.5: The term "Data Monitoring Committee" was changed to "Safety Monitoring Committee" as the description is more accurate.

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Synopsis and Section 10.2.5.1 Primary Efficacy Analysis: Corrected the Ha to ORR>**32**%.

Synopsis and Section 10.2.5.2 Secondary Efficacy Analysis: Deleted text describing an analysis of hematologic improvement was deleted as the proposed analysis is not for any study endpoints.

Section 1.4, Section 1.5, and Section 1.6: Text updated with the most recent BGB-3111 clinical data.

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Table 2 Study Assessments: An echocardiogram was added at screening due to the new inclusion criterion #18 (LVEF ≥50%)

Table 2 Study Assessments footnote #5 and Section 7.2.1 Demography: Removed race/ethnicity from demography as all patients in this study are Chinese.

Section 6.5: Revised the BGB-3111 dose reduction table for additional clarity.

Section 6.5.1: Corrected decreased absolute neutrophil count adverse event definition to CTCAE Grade 4 ($<0.5x10^9$/L) lasting >**10** days, and updated the dose reduction criteria for hematologic toxicity.

Section 6.5.2: Updated the dose reduction criteria for non-hematologic toxicity.

Section 7.3.1 and Appendix 3: The response criteria for CLL were clarified.

Section 7.3.1.1 and Section 7.3.1.4: Measurement method for both lymphadenopathy and hepatomegaly/splenomegaly were changed to CT scan for consistency with Hallek 2008, and for this to be an objective assessment.

Section 7.3.1.1, Section 7.3.1.7, and Appendix 3: Revised the CR criteria for capturing non-target lesions and PD criteria for single node and non-target lesions.

Section 7.3.2: The response criteria for SLL were clarified and a new separate appendix for the response criteria was added (Appendix 4).

Section 7.4.1: Revised AE reporting language for consistency with Section 9.2.2.

Section 7.4.4.1: The hematology evaluation during the study was clarified.

Section 7.4.5, Section 10.3.5, and Table 2 Schedule of Assessments: The frequency of electrocardiograms (ECGs) was revised.

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Section 9: Safety monitoring and reporting were updated for consistency with other BeiGene protocols.

Section 9.1.1: Deleted text describing treatment-related lymphocytosis, as this is included in Section 7.4.1

Section 9.2.21: Clarified that adverse events will be collected until 30 days after the last dose of BGB-3111 regardless of disease progression or the start of anti-cancer therapy, for consistency with other BGB-3111 protocols.

Section 10.2.3 and Section 10.2.5.4: Removed the treatment-naïve, race, and geographic regions variables to be summarized as all patients in this study are Chinese and have relapsed/refractory CLL/SLL.

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Section 10.3.2: This section was revised to be consistent with the secondary endpoints, and modified the definition of treatment-emergent adverse event (TEAE) for consistency with other BeiGene protocols.

Appendix 3 CLL Response Definitions: Revised the table to specify the response criteria for bone marrow and to clarify the response definitions in the footnotes.

Appendix 8 (New York Heart Association Functional Classification) was added to aid study personnel.

SYNOPSIS

Name of Sponsor/Company:	**BeiGene (Beijing) Co., Ltd**
Name of Finished Product:	**BGB-3111**
Name of Active Ingredient:	**BGB-3111**
Title of Study:	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
Protocol No:	BGB-3111-205
Study duration: Screening (up to 28 days); subjects will receive daily treatment on study for up to 3 years or until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination by sponsor; safety follow up for 30 days after drug termination; survival follow up until study termination.	Phase: 2

Objectives:

Primary:

To evaluate the efficacy of BGB-3111 at a dose of 160 mg orally (PO) twice daily (BID), in subjects with relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) as assessed by an Independent Review Committee (IRC) using the overall response rate according to modified International Workshop on CLL (IWCLL) Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013) and the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014).

Secondary:

To evaluate the efficacy of BGB-3111 as measured by progression free survival (PFS), duration of response (DOR), and time to response (TTR) by IRC.

To evaluate the efficacy of BGB-3111 by investigator as measured by overall response rate.

To evaluate the safety and tolerability of BGB-3111 at a dose of 160 mg PO BID in subjects with R/R CLL/SLL.

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Methodology:

This is an open-label, single-arm, multicenter Phase 2 study.

Planned no. of subjects:	Approximately 80 subjects will be enrolled.

Study Population	Inclusion criteria: 1. Confirmed diagnosis of CLL/SLL. a. Each clone of leukemia cells is restricted to expression of either κ or λ light chains. Cells co-express CD5 along with at least one B-cell surface marker (CD19, CD20, or CD23) b. Prolymphocyte ≤ 55% of lymphocytes in peripheral blood c. Cyclin D1 immunohistochemistry or fluorescence in situ hybridization for t(11;14) should be done in cases with an atypical immunophenotype d. Central pathology confirmation by the lead PI must be performed before a subject can be enrolled on study 2. Meeting at least one criterion for treatment according to IWCLL 3. Men and women ≥18 years of age 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 5. Measurable disease by contrast enhanced computerized tomography/magnetic resonance imaging (CT/MRI). Measurable disease is defined as at least 1 lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions. 6. Previously treated with a minimum of 1 prior line of standard chemotherapy-containing regimen (with completion of ≥2 treatment cycles). For example: • Two cycles of fludarabine, cyclophosphamide, rituximab • Two cycles (8 weeks) or a total dose of 500 mg of oral chlorambucil 7. Documented failure to achieve at least partial response (PR) or documented disease progression after response to the most recent treatment regimen. Refractory disease is defined as treatment failure (stable disease, non-response, progressive disease [PD]) or disease progression within 6 months after the most recent prior therapy (Hallek et al, 2008). 8. Neutrophils ≥ 0.75 x 10^9/L independent of growth factor support within 7 days of study entry 9. Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of study entry 10. Creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]) 11. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN 12. Bilirubin ≤2 x ULN (unless documented Gilbert's syndrome)

	13. International normalized ratio (INR) ≤1.5 and activated partial thromboplastin time (APTT) ≤1.5 x ULN. If a factor inhibitor is present with prolongation of the INR or APTT, a patient may be enrolled after consultation with the medical monitor. 14. Subjects may be enrolled who relapse after autologous stem cell transplant if they are at least 6 months after transplant. To be eligible after transplant, subjects should have no active related infections 15. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control can be defined as abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for up to 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or utilize a barrier method where the female partner utilizes the effective forms of birth control noted above. 16. Life expectancy of >4 months 17. Able to provide written informed consent, can understand and comply with the requirements of the study 18. Echocardiogram (ECHO) must demonstrate left ventricular ejection fraction (LVEF) ≥50%; (AHA, 2016) Exclusion criteria: 1. Current or history of central nervous system (CNS) lymphoma 2. Prior exposure to a BTK inhibitor 3. Prior corticosteroids given in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days. Prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, antineoplastic therapy with Chinese herbal medicine or antibody based therapies within 4 weeks of the start of study drug. 4. Major surgery within 4 weeks of screening 5. Not recovered from toxicity of any prior anti-cancer therapy to ≤Grade 1 (except for alopecia, absolute neutrophil count (ANC) and platelets. For ANC and platelets, please follow inclusion criteria #8 [neutrophils] and #9 [platelets]) 6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent 7. Currently active clinically significant cardiovascular disease

such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (see Appendix 8) or history of myocardial infarction within 6 months of screening

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

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA < 1000 IU/mL and anti-viral therapy during study and perform monthly monitoring of HBV DNA	HBsAg(-) HBcAb(+)	HBV DNA>1000 IU/ml
HCV	Antibody (-)			
	Antibody (+)	HCV RNA "Not detected" (<15 IU/mL) Perform monthly monitoring of HCV RNA	Antibody(+)	HCV RNA Detected

12. Pregnant or lactating women
13. Any life-threatening illness, medical condition or organ system

	dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk 14. Requires ongoing treatment with any medication which is a strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitor or strong CYP3A inducer 15. Known or clinically suspected Richter's transformation at the time of study entry 16. History of stroke or intracranial hemorrhage within 6 months prior to enrollment 17. Has received allogenic hematopoietic stem cell transplantation prior to enrollment
Test product, dose and mode of administration:	BGB-3111 160 mg (two – 80-mg white opaque capsules) PO BID
Reference therapy, dose, and mode of administration:	Not applicable

Study Treatment:

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

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

Table 1. BGB-3111 Dose Reduction for Toxicity Occurrence

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

BID, twice a day; QD, daily

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

Dose Reductions for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting >10 days, but if medically indicated, can stop BGB-3111 earlier)
- Grade 4 thrombocytopenia (lasting ≥ 10 days, but if medically indicated, can stop BGB-3111 earlier)
- ≥ Grade 3 neutropenia with fever
- ≥ Grade 3 thrombocytopenia with significant bleeding

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

Dose Reductions for Non-Hematologic Toxicity

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

Concomitant Therapy and Clinical Practice:

Prohibited Concomitant Therapy

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

Drugs known to prolong the QT/QTc interval are prohibited

Drugs known to prolong the QT/QTc interval should be avoided, in accordance with the Food and

Drug Administration (FDA) Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. A list of drugs with QTc prolongation potential is provided in Appendix 2. If a patient requires treatment with any of these medications on study, and a non-QT prolonging alternative medication is not available, the medical monitor must be notified. Upon written approval by the medical monitor, treatment with study drug should be withheld immediately and recommenced to restart study drug at least 5 half-lives following the last use of the QT prolonging medication.

Concomitant Use of CYP Inhibiting/Inducing Drugs

Information about clinical drug interactions with BGB-3111 is not available. Based on available nonclinical metabolism data, BGB-3111 is primarily metabolized by CYP3A. Avoid concomitant administration of BGB-3111 with strong CYP3A inhibitors or strong CYP3A inducers (refer to Appendix 5 for a list of these medications). Grapefruit juice and Seville oranges should be avoided, as they may affect the metabolism of BGB-3111. For short-term use (treatment for ≤7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting BGB-3111 therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations.

BGB-3111 is a moderate inhibitor of the human isoenzymes CYP2C8, CYP2C9, and CYP2C19. Drugs that are primarily metabolized by these isoenzymes should be used with caution when administering BGB-3111, with monitoring of drug concentrations as appropriate (refer to Appendix 6 for examples of these medications).

Criteria for Evaluation:

Response will be based on IRC evaluation in accordance with modified IWCLL Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013) for subjects with CLL and the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014). The tumor assessment will be performed every 12 weeks during the first 48 weeks and then every 24 weeks thereafter. Bone marrow biopsy will be required for confirmation of complete response ([CR] at first occurrence of radiological and clinical evidence of CR) in subjects with bone marrow tumor involvement prior to study drug. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.

An IRC will be established for response evaluation and details will be provided in the IRC charter.

The safety of this study will be monitored by a Safety Monitoring Committee (SMC); its organization and detailed execution will be written in the SMC charter. The SMC will evaluate safety data and will provide advice accordingly. Subjects will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI CTCAE v. 4.03]) and serious AEs (SAEs).

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

Subjects who, at time of progression, have an ongoing AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable or the subject is lost to follow-up.

Endpoints:

Primary Endpoint:

The primary endpoint of the study is the overall response rate, as determined by IRC defined as follows:

- CLL: achievement PR, including nodular partial response (nPR), and partial response with lymphocytosis (PR-L), CR, or CR with incomplete blood count recovery (CRi) according to modified IWCLL Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013), and
- SLL: CR and PR according to the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014)

Secondary Endpoints:

Efficacy (using response assessment as determined by IRC):

- Progression-free survival (PFS): time from treatment initiation to first documentation of progression by IWCLL criteria/revised criteria for response for malignant lymphoma or death, whichever is earlier
- DOR: time from the first response documentation according to above response criteria to the date that PD is objectively documented or death, whichever is earlier
- TTR: time from treatment initiation to first signs of response
- ORR by investigator: overall response rate as determined by investigator

Safety:

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

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

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Statistical Methods:

Populations:

The Safety Population (SP) includes all subjects who received any dose of BGB-3111. This will be the primary population for the efficacy and safety analyses.

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

The PK Population includes all subjects for whom valid BGB-3111 PK parameters can be estimated.

Primary Efficacy Analysis:

The primary efficacy endpoint is the overall response rate (ORR) for subjects with CLL, according to modified IWCLL criteria (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013) and SLL, according to the 2014 Revision for Malignant Lymphoma (Cheson et al, 2014), as assessed by IRC.

The ORR is defined as the proportion of subjects achieving a best overall response (BOR) of CR, CRi, nPR, PR, or PR-L for CLL patients, and CR or PR for SLL patients, per IRC prior to initiation of subsequent antineoplastic therapy.

In this population, ORR in the historical control is assumed to be approximately 32% based on recent trials. The ORR in this study is estimated as 63%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: ORR=32%

Ha: ORR >32%

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

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

The best overall response (BOR) is defined as the best response recorded from the start of BGB-3111 until data cut or start of new antineoplastic treatment. Subjects with no post-baseline response assessment (due to whatever reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, CRi, nPR, PR, PR-L, SD, and PD /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 subject received the first dose of study drug. Subsequent analyses will be performed when mature secondary efficacy endpoints are available, and will be based on the Safety Population.

Secondary Efficacy Analysis:

The Kaplan-Meier (KM) method will be used to estimate progression event-free curves and corresponding quantiles (including the median). The two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer et al, 1982). The PFS rate at 6 months, defined as the percentages of subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926).

The PFS censoring rule will follow 国家食品药品监督管理局的《抗肿瘤药物临床试验终点技术指导原则》(2012).

The DOR is defined as the time from the date that the response criteria (CR, CRi, PR, or PR-L) are first met to the date that PD is objectively documented or death, whichever occurs first. Subjects who do not have disease progression will be censored at their last valid assessment. The TTR is defined as time from the starting date of BGB-3111 to the date the response criteria are

first met. The DOR will be similarly analyzed using the KM method as described above. The KM estimates of DOR will be plotted over time. The TTR will be summarized using sample statistics such as sample mean, median, and standard deviation.

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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 v.4.03. All treatment-emergent AEs (TEAEs) will be summarized. A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Serious adverse events, deaths, TEAEs with Grade 3 or above, TEAEs that led to treatment discontinuation, and treatment related AEs, dose reduction or dose interruption will also be summarized.

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

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

Sample Size:

Approximately 80 subjects will be enrolled.

The sample size calculation was based on the level of precision of the estimated ORR. The 95% CI of response rate is (51.5%, 73.5%) with 80 subjects assuming a 63% response rate. The power of demonstrating statistical superiority over historical control rate (ie, 32%) is greater than 0.99 in a binomial exact test at a 1-sided alpha of 0.025 at the assumed response rate of 63%.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antigen-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AEs	adverse events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
ASH	American Society of Hematology
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
CCI [redacted]	[redacted]
AV	atrioventricular
BCR	B-cell receptor
BID	twice a day
BOR	best overall response
BTK	Bruton's tyrosine kinase
CERT	Center for Education and Research on Therapeutics
CI	confidence interval
CL/F	apparent total clearance of the drug from plasma after oral administration
CLL	chronic lymphocytic leukemia
CCI [redacted]	[redacted]
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete blood count recovery
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome

CYP3A	cytochrome P450, family 3, subfamily A
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FGR	Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
GCP	Good Clinical Practice
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HDPE	high density polyethylene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
CCI	[redacted]
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IRC	Independent Review Committee
IRB	Institutional Review Board
ITK	interleukin-2-inducible T cell kinase
IV	intravenous

IWCLL	International Workshop on Chronic Lymphocytic Leukemia
JAK3	Janus kinase 3
KM	Kaplan-Meier
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LDI	longest diameter of a lesion
LDL	low density lipoprotein
LDT	lymphocyte doubling time
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nPR	nodular partial response
ORR	overall response rate
CC	[redacted]
PCR	polymerase chain reaction
PD	progressive disease
PI	principal investigator
PO	orally
PFS	progression-free survival
PI3Kδ	delta isoform of phosphoinositide-3-kinase
CC	[redacted]
PP	Per-protocol Population
PR	partial response
PR-L	partial response with lymphocytosis
PT	preferred term or prothrombin time
QD	daily
QT	interval between the beginning of the QRS complex to the end of the T wave
RNA	ribonucleic acid
R/R	relapsed or refractory

SAEs	serious adverse events
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOC	system organ class
TEAEs	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TP53	tumor protein 53
TTR	time to response
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia
X	to be performed
ZAP-70	Zeta-chain-associated protein kinase 70

1 INTRODUCTION

1.1 Current Status of Chronic Lymphocytic Leukemia Care

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the Western world, in 2016, there were 18,960 new cases of CLL diagnosed, making up 24-38% of all leukemias, the incidence rate is 5-6/10,000 population (Siegel et al, 2015), with 4,660 dying from this disease in the same year (Hallek et al, 2015). In 2015, the Chinese cancer registry recorded 88,200 new lymphoma cases (Chen et al, 2016), of which 3704 were CLL, refractory and resistant cases are even fewer. The median age of occurrence of CLL is between 67 and 72, but is trending towards younger patients, with a predominance of males (1.7:1) over females. It is generally considered to be incurable with conventional doses of chemotherapy. Until recently there has been little enthusiasm for more aggressive approaches to this often indolent disease. However, with the advent of purine analogues and the high complete remission rates they bring, new interest has been kindled in the management of this disorder.

With the advent of "routine" blood tests, many patients are now being diagnosed while still asymptomatic. The most common complaints of symptomatic patients are fatigue, weight loss, fevers, frequent bacterial and viral infections, and increased tendency to bleed. On physical examination lymphadenopathy and splenomegaly are often found. Laboratory evaluation reveals an excess of mature appearing lymphocytes in the peripheral blood. These leukemic cells have a B cell immunophenotype and their development is arrested in a functionally immature state. The patient may also have thrombocytopenia and anemia. (Hallek et al, 2015).

The Chinese Lymphoma Pathology Association initiated a multi-institutional collaborative effort, a retrospective analysis of 10,002 lymphoma cases was performed. Of 6,632 non-Hodgkin's lymphoma (NHL) cases, there were only 424 CLL, making up 4.2% of all lymphoma cases, and 6.4% of NHL (李小秋 2012). In 2015, the Chinese Cancer Registry reported on 88,200 new lymphoma diagnoses (Chen et al, 2016), around 3704 CLL cases, relapsed or refractory (R/R) will be even fewer. Compared to CLL, small lymphocytic lymphoma (SLL) is even rarer (Lymphoma Information Network).

In Beijing, CLL makes up 4.6% of all leukemias (Boggs et al, 1987), incidence of $0.5/10^5$ (Yang et al, 1991). According to GLOBOCAN 2012, CLL in China should come to 1766 new cases annually.

The diagnosis of CLL is made by a combination of morphologic and immunophenotypic criteria. Different diagnostic criteria have been set forth by several organizations. The National Cancer Institute (NCI)-sponsored working group produced guidelines for CLL clinical protocols. The diagnostic criteria require that leukemic cells appear mature (morphologically resembling small lymphocytes) and that no more than 55% be atypical lymphocytes, prolymphocytes, or lymphoblasts. The predominant cells co-express B cell markers with CD5 antigen in the absence of other T cell antigens, express either kappa or lambda light chains, and have low density surface lmmunoglobulin on the cell surface. Other criteria include a minimal absolute lymphocyte count of 5,000/mm^3, a bone marrow aspirate demonstrating ~ 30% of all nucleated cells are lymphoid, and the exclusion of other lymphoproliferative disorders (International CLL-IPI working group, 2016).

The Rai staging criteria, as originally proposed, grouped patients on the presence or absence of lymphadenopathy (Stage I), splenomegaly and/or hepatomegaly (Stage II), anemia (Stage III), or thrombocytopenia (Stage IV). Patients with only a lymphocytosis were classified Stage 0. The original Rai system was later modified to reduce the number of stages from five to three, without altering its prognostic capabilities (Cheson et al, 2014). Patients with a good prognosis (Rai Stage 0) have a median survival of more than 12.5 years while intermediate risk patients (Rai Stage I and II) have worse prognosis with a median survival of less than 8 years. High risk patients (Rai Stage III and IV) have an expected survival of between 1.5 and 2.5 years (International CLL-IPI working group, 2016).

Other prognostic indicators include: absolute blood lymphocyte count, bone marrow histological patterns, cytogenetics, lymphocyte doubling time (LDT), lactate dehydrogenase levels, beta-2 microglobulin, lymphocyte morphological subtypes, age, sex, and response to treatment (International CLL-IPI working group, 2016). Patients with LDT of 12 months or less have a significantly worse prognosis than patients with a longer LDT. Somatic hypermutation of immunoglobulin heavy chain variable region (IGHV) genes is seen in about 50% of patients and have a more favorable prognosis compared to patients who are unmutated. Expression of zeta-chain-associated protein kinase 70 (ZAP-70) is a surrogate for immunoglobulin variable region mutations and ZAP-70 expression directly correlated with unmutation IGHV. Trisomy 12 and 17p (p53) chromosomal deletion also correlated with poor prognosis. Expression of CD38 on CLL cells has also been associated with a poor prognosis (Vollbrecht et al, 2015).

While partially related to stage, the pattern of infiltration of the bone marrow reflects the total burden of disease. Patients with a diffuse pattern (vs nodular or interstitial) have a less favorable

prognosis (Stilgenbauer et al, 2015). A high absolute blood lymphocyte count, high lactate dehydrogenase (LDH), older age, male gender, increased percentage of prolymphocytes, and poor response to treatment also portend for a poor prognosis. These prognostic indicators are more useful in early stage disease where there appears to be a subgroup of patients who have prolonged periods without disease progression. Efforts have been made to define a group of patients with "smoldering CLL" who have a prognosis that approximates that of the general population. Criteria that have been identified include peripheral blood lymphocyte doubling time greater than 12 months; non-diffuse bone marrow infiltration; absolute lymphocyte count $<30 \times 10^9/mm^3$ and hemoglobin (Hb) >13 g/dL (Stilgenbauer et al, 2015).

As CLL remains largely an incurable disease, treatment will usually be initiated with palliative intent, and therefore, should not necessarily begin at the time of diagnosis. Studies to date have not demonstrated an improvement in survival with early intervention when compared to treating later in the course of the disease (de Claro et al, 2015). In general, treatment should begin when the patient becomes symptomatic or there is evidence of frank progression of disease. As outlined above, symptoms include fever, excessive fatigue, weight loss, and symptomatic enlargement of either lymph nodes or spleen. These symptoms are all relative indications for treatment and the urgency for initiating therapy will depend on the magnitude of the symptoms. For instance, minor well-tolerated lymphadenopathy does not mandate treatment. Infections are common in CLL and, consequently, may not necessarily be an indication to start cytotoxic therapy. In fact, patients having difficulty with recurrent infections as a consequence of disease-induced hypogammaglobulinemia may benefit from infusional therapy with intravenous (IV) gamma globulin. However, impaired bone marrow function, as evidenced by anemia, thrombocytopenia, or granulocytopenia caused by marrow infiltration by malignant cells definitely warrants specific treatment. Other life-threatening events include lymphadenopathy that compromises vital organs, autoimmune destruction of either platelets or red cells, and transformation of the CLL to a more aggressive malignancy. Finally, if patients are considering enrollment in an investigational therapeutic trial (eg, bone marrow transplantation following cytotoxic therapy), treatment might be initiated earlier (de Claro et al, 2015).

Recent significant advances in the management of CLL have also been made, particularly with the development and availability of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. The introduction of ibrutinib therapy will likely have a dramatic impact on the treated natural history of CLL. Prior to the introduction of ibrutinib, treatment for CLL was based on chemotherapy, particularly the alkylating agents chlorambucil, cyclophosphamide, and, more recently,

bendamustine. Randomized control trials with chlorambucil as the control arm of new agents in chemo-naive CLL patients have resulted in significantly improved overall response rates and progression-free survival (PFS), but insignificant or minor improvements in overall survival (OS). Chlorambucil overall response rate / complete response (CR) rates / PFS time reported was 55%/2%/14.7 months against alemtuzumab's 83%/24%/23.3 months (Hillmen et al, 2008) 31%/2%/8.3 months against bendamustine's 68%/31%/21.6 months (Knauf et al, 2009); 31%/0%/11.1 months, against rituximab-chlorambucil's 65.7%/7.3%/16.3 months, against obinotuxumab-chlorambucil's 77.3%/22.3%/26.7 months (Goede et al, 2014); 35%/4%/18.9 months against 86%/4%/not reached for ibrutinib.

In the 1990s, the purine analogue fludarabine was shown in clinical trials to improve response rates to 51-74%, and duration of response (DOR) up to 22.9 months for chemo naïve patients (Keating et al, 1998) compared to chlorambucil, it became a standard initial therapy in younger patients with CLL. The addition of anti-CD20 antibodies to the armamentarium for CLL has also resulted in incremental improvements in PFS in the initial therapy setting. With adoption of FCR (fludarabine, cyclophosphamide, and rituximab) as the highest standard of care for suitably fit CLL patients, overall response rate of 95%, complete response in 72% (Keating et al, 2005). At a median follow up time of 11.8 years for the initial 300 patients, 97 (32%) have ongoing remissions, 23 (7.7%) died whilst still in remission from other illnesses, 143 (47%) relapsed, 13 (4.3%) were refractory, 22 (7.5%) transformed into an aggressive Richter's syndrome, MDS, AML, ALL, or LGL (Tam et al, 2014). Realistically, the choice of initial therapy in CLL is dictated by patient age and existence of comorbidities (Else et al, 2015).

The treatment standards for CLL, however, are in transformation because of the advent and development of effective inhibitors of B cell receptor signaling (Byrd et al, 2013; Byrd et al, 2014). Blockade of the B cell receptor signaling cascade by inhibition of either BTK or the delta isoform of phosphoinositide-3-kinase (PI3Kδ) causes profound inhibition of proliferative signaling from CLL cell-host interactions and results in frequent and durable responses in patients with both relapsed/ refractory and treatment-naïve CLL. While the use of PI3Kδ inhibitors are often limited by toxicities including hepatotoxicity, colitis, and infectious complications, particularly in treatment-naïve patients, the BTK inhibitor ibrutinib has a highly favorable tolerability profile when compared to conventional therapies. Ibrutinib has been shown in randomized trials to significantly improve PFS vs the anti-CD20 antibody ofatumumab in relapsed and refractory patients (Byrd et al, 2014) and versus chlorambucil in treatment-naïve patients (Burger et al, 2015). Additionally, both trials demonstrated a significant overall survival

advantage for the groups randomized to receive ibrutinib, despite allowance of crossover treatment for control arm patients. These results have had a dramatic effect on the treatment standards for CLL, especially for those patients who are not candidates for intensive therapy (Cramer et al, 2015; Stadler et al, 2016; Bachow et al, 2016).

Nonetheless, Phase 3 trials and long-term single-center follow-up studies have elucidated the limitations and patterns of failure of ibrutinib therapy for CLL. In the Phase 3 trial of ibrutinib versus ofatumumab in subjects with R/R disease (or treatment-naïve disease bearing del17p), with a median follow-up of 9.4 months, of 195 subjects assigned to receive ibrutinib, 27 subjects (14%) discontinued therapy, 9 for disease progression (including Richter's transformation), 8 for adverse events (AEs), 8 for death, and 2 for other reasons (Byrd et al, 2014). In the randomized trial of ibrutinib versus chlorambucil in subjects with treatment-naïve CLL, at a median follow-up of 18.4 months, of 136 subjects assigned to receive ibrutinib, 17 subjects (13%) discontinued treatment, predominantly for adverse event or death (n=14) rather than disease progression (n=2). In a large single-center experience with ibrutinib treatment in CLL (n=127), with a median treatment duration of 13 months, 33 subjects (26%) had discontinued ibrutinib. Discounting discontinuation for proceeding to transplant (n=3) or miscellaneous reasons (n=2), the number of discontinuations for progressive disease (PD)/ transformation versus adverse events/ death were identical (n=14 for each; Jain et al, 2015). These results are consistent with a larger single-center experience (n=308), in which, at a median follow-up of 20 months, 76 subjects (25%) had discontinued therapy, 31 subjects for disease progression and 45 for non-progression reasons. Adverse events were most common amongst the non-progression discontinuations, and could be divided into infectious complications (n=28) and non-infectious events (n=17). Of the subjects with relapse in whom sequencing was performed (n=11), all cases were characterized by the presence of BTK or phospholipase C γ mutation (Maddocks et al, 2015). In summary, despite the high level of activity and tolerability of ibrutinib in patients with CLL, treatment discontinuation is not uncommon, and both disease progression and treatment-emergent adverse events (TEAEs) contribute to this experience. The results suggest that improvements in both efficacy and safety are needed in order to optimize BTK inhibitor therapy in CLL.

Treatment with BTK inhibitors can incur transient increase in lymphocytes in over 80% of CLL and 40% of mantle cell lymphoma (MCL) patients. Absolute lymphocyte counts generally peak around 4 weeks, and take 4-7 months to return to baseline. This lymphocytosis is generally asymptomatic, requires no medical management, and does not signify disease progression,

therefore treatment with the B cell inhibitors should be continued (Chang et al, 2013; Woyach et al, 2014).

In the US, Food and Drug Administration (FDA)-approved drugs for the treatment of CLL include: chlorambucil (1957). cyclophosphamide (1959), fludarabine (1991), alemtuzumab (2007), bendamustine (2008), ofatumumab (2009), ibrutinib (2013), rituximab, FCR (2010), and obinutuzumab (2013). However, in China, only the following listed drugs are approved:

CLL	Phase	2nd line	Patients (n)	ORR (CR)	Reference
Chlorambucil	2	v		7% （Fludarabine treated）	
Rituximab	3	V	110	13% (0%)	Furman et al, 2014
Fludarabine	2	V	703	32% （3%）	Sorensen et al, 1997
FCR (young, fit, no p53 loss)	2	v	284	74% (30%）	Badoux et al, 2011

Abbreviations: CLL; chronic lymphocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide, and rituximab; ORR, overall response rate

Therefore, finding new, more potent, easy to administer drugs with a good safety and tolerability profile is of the utmost priority.

1.2 BGB-3111

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

1.3 Non-Clinical Data

BGB-3111 inhibits BTK with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nanomolar (nM) in biochemical assays. Cellular assays confirmed that BGB-3111 inhibited B-cell receptor (BCR) aggregation-triggered BTK autophosphorylation, and blocked downstream phospholipase C-beta-2 signaling in MCL cell lines. BGB-3111 potently and selectively inhibited cellular growth of several MCL cell lines (REC-1, Mino and JeKo-1) and activated B-cell (ABC) type of

diffuse large B-cell lymphoma cell line TMD8, with IC_{50}s from 0.36 nM to 20 nM, while inactive in many other hematologic cancer cell lines. In vivo studies showed that BGB-3111 induced dose-dependent anti-tumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. BGB-3111 was more selective than ibrutinib for inhibition of kinase activity of BTK vs. EGFR, Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), fyn-related kinase (FRK), human epidermal growth factor receptor (HER)2, HER4, ITK, JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and TEC. Cellular assays also confirmed that BGB-3111 is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antigen-dependent cell-mediated cytotoxicity (ADCC). BGB-3111 was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced ADCC, consistent with BGB-3111 being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays, thus preventing the potential for antagonism with rituxan that has been seen preclinically with other BTK inhibitors.

1.4 Phase 1 Clinical Experience

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

1.5 BGB-3111 in R/R CLL in a Global Clinical Trial

As of the data cut on October 3, 2016, 63 CLL/SLL patients have been enrolled, 46 patients have been followed for a median of 8.6 months, and have undergone at least one evaluation to be included in the efficacy analysis. One patient discontinued therapy for an adverse event prior to first evaluation; all of the remaining subjects are still on study. One patient (2%) has stable disease (SD), 31 (67%) have partial response (PR), and 13 (28%) have partial response with lymphocytosis (PR-L). Of the 46 patients, the median age is 67 years (24-79), Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 in 45 patients, 9 are chemo-

naive, 37 have received at least one prior treatment regimen, and 11% have bulky disease. Molecular risk factors evaluated demonstrated 6/34 (18%) to have del 17p or p53 mutation, 12/34 (35%) have 11q deletion, and 9/12 (75%) have unmutated IgHv. As for toxicity reported, Grade 3-4 adverse events were 1(2%) petechiae/purpura/contusion, and 4(9%) neutropenia. Grade 3-4 adverse events of interest included 1 patient (2%) with hemorrhage and 1 patient (2%) with atrial fibrillation.

1.6 BGB-3111 Phase 1 Clinical Trial in China

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

1.7 Pharmacokinetics and Pharmacodynamics

In the first-in-human, Phase 1 study (BGB-3111-AU-003), the PK of BGB-3111 was linear between 40 mg and 320 mg daily administered orally (BGB-3111 Investigator's Brochure [IB]). The absorption of BGB-3111 is rapid with median time to maximum plasma concentration of 2 hours. The terminal elimination half-life is approximately 4 hours at 320 mg daily. Results from a food effect study showed that BGB-3111 exposure was not altered by a high-fat breakfast, and mean area under the plasma concentration time curve (AUC) and maximum observed plasma concentration (C_{max}) were increased by 12% and 51%, respectively, with a standard breakfast when compared to fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg administered daily in the ongoing Phase 1 study, and was not associated with any new safety findings, therefore BGB-3111 can be administered with or without food.

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

1.8 Use of BGB-3111 in CLL

Bruton's tyrosine kinase, a member of the TEC family kinases, is a critical component of the BCR signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib, the first-in-class FDA-approved BTK inhibitor, has demonstrated promising anti-tumor activity in CLL.

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

For these reasons, we believe that a single-arm Phase 2 open-label study of the BTK inhibitor BGB-3111 in subjects with CLL is warranted.

The lack of treatment-related SAEs and preliminary efficacy results from the Phase 1 study supports further investigation of 160 mg BID in subsequent Phase 2 and Phase 3 studies to confirm the benefit/risk profiles of BGB-3111 in CLL/SLL. Refer to the IB for more detailed information on the background of BGB-3111.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of BGB-3111 at a dose of 160 mg PO BID, in subjects with R/R CLL/SLL as assessed by an Independent Review Committee (IRC) using the overall response rate (complete response, including CRi, and PR, including nodular PR [nPR], and PR-L) for subjects with CLL according to modified International Workshop on CLL (IWCLL) Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013; see Appendix 3) and CR and PR for subjects with SLL according to the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014; see Appendix 4).

2.2 Secondary Objectives

Efficacy:

- To evaluate the efficacy of BGB-3111 as measured by PFS, DOR, and time to response (TTR) by IRC
- To evaluate the efficacy of BGB-3111 by investigator as measured by overall response rate.

Safety:

- To evaluate the safety and tolerability of BGB-3111 at a dose of 160 mg PO BID in subjects with R/R CLL/SLL

2.3 CCI

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study is the overall response rate, as determined by IRC, defined as the achievement of PR, including nPR, PR-L, complete response (CR), or CRi according to modified IWCLL Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013; see Appendix 3), and CR and PR according to the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014; see Appendix 4).

3.2 Secondary Endpoints

Efficacy (using response assessment as determined by IRC):

- PFS: time from treatment initiation to first documentation of progression or death, whichever is earlier
- DOR: time from the first response documentation according to above response criteria to the date that PD is objectively documented or death, whichever is earlier
- TTR: time from treatment initiation to first signs of response
- ORR by investigator: overall response rate as determined by investigator

Safety:

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

- The incidence and severity of TEAEs, SAEs, and treatment-related AEs according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03
- The incidence, severity, and causation of adverse events leading to study drug discontinuation

3.3 CCI

[redacted]

3.4 Rationale for Endpoint Selection

Efficacy: The proposed endpoints have been chosen based on relevance to the pathophysiology and clinical manifestations of CLL, and the known pharmacology of BGB-3111 as a BTK inhibitor. The goal of this study is to exemplify the benefit/risk ratio of BGB-3111. All of the endpoints have been explored in prior studies of chronic lymphocytic leukemia treatment, and

data derived from this Phase 2 trial can be compared with historical data with acceptable reliability and accuracy.

Safety and tolerability: Small molecule TKIs have been known to induce QT prolongation. BGB-3111 did not incur any such toxicity in its first 39 patients enrolled in the Phase 1 study in Australia, however, continued vigilance is necessary. Off-target inhibition resulting in impaired platelet function and bleeding is another adverse event of interest. In addition, the hematological toxicity with Grade 3/4 neutropenia and infection needs to be documented.

4 STUDY DESIGN

4.1 Summary of Study Design

This is a single-arm, open-label, multicenter Phase 2 study in subjects with histologically documented CLL/SLL who have relapsed after ≥1 prior treatment regimen(s). The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase. Subjects who have not progressed at the time of the final analysis and/or study closure, or subjects who had disease progression but are still benefitting from BGB-3111 treatment in the assessment of the investigator, will be considered for participation in the long-term extension study.

Approximately 80 subjects will be enrolled. The primary efficacy analysis will be conducted no later than 12 months after the last subject received the first dose of study drug. Response will be evaluated by IRC review in accordance with the 2008 International Working Group on CLL Guidelines for subjects with CLL (Appendix 3) and the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Appendix 4). Assessment by computed tomography (CT) scan will occur every 12 weeks during the first 48 weeks, and then every 24 weeks until disease progression or end of study, whichever comes first. Tumor response data collection will continue until disease progression in any subject that ends BGB-3111 treatment prior to disease progression.

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

Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations.

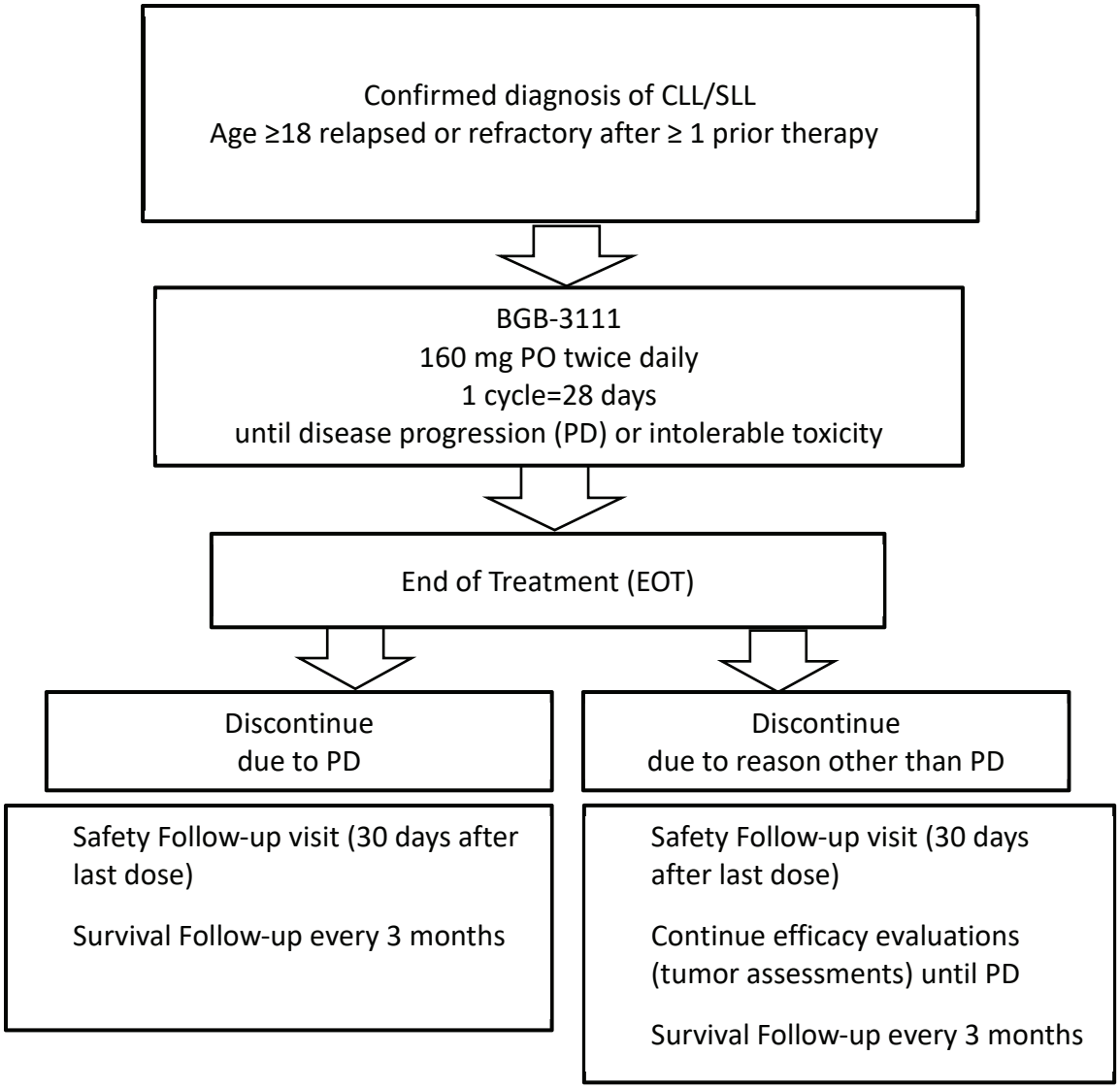
Please refer to Table 2 for details on screening procedures. Screening evaluations can be repeated within the screening period.

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

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

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

Figure 1 Schema for Study BGB-3111-205



5 STUDY POPULATION

5.1 Inclusion Criteria

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

1. Confirmed diagnosis of CLL/SLL:
    a. Each clone of leukemia cells is restricted to expression of either κ or λ light chains. Cells co-express CD5 along with at least one B-cell surface marker (CD19, CD20, or CD23)
    b. Prolymphocyte ≤55% of lymphocytes in peripheral blood
    c. Cyclin D1 immunohistochemistry (IHC) or fluorescence in situ hybridization for t(11;14) should be done in cases with an atypical immunophenotype
    d. Central pathology confirmation by the lead PI must be performed before a subject can be enrolled on study
2. Meeting at least one criterion for treatment according to IWCLL
3. Men and women ≥18 years of age
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
5. Measurable disease by contrast enhanced computerized tomography/magnetic resonance imaging (CT/MRI). Measurable disease is defined as at least 1 lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions.
6. Previously treated with a minimum of 1 prior line of standard chemotherapy-containing regimen (with completion of ≥2 treatment cycles). For example:
    - Two cycles of FCR
    - Two cycles (8 weeks) or a total dose of 500 mg of oral chlorambucil
7. Documented failure to achieve at least PR or documented disease progression after response to the most recent treatment regimen. Refractory disease is defined as treatment failure (SD, non-response, PD) or disease progression within 6 months after the most recent prior therapy (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013)
8. Neutrophils ≥ 0.75 x 10^9/L independent of growth factor support within 7 days of study entry

9. Platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of study entry

10. Creatinine clearance of ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD])

11. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN

12. Bilirubin ≤2 x ULN (unless documented Gilbert's syndrome)

13. International normalized ratio (INR) ≤1.5 and activated partial thromboplastin time (APTT) ≤1.5 x ULN. If a factor inhibitor is present with prolongation of the INR or APTT, a patient may be enrolled after consultation with the medical monitor.

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

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

16. Life expectancy of > 4 months

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

18. Echocardiogram (ECHO) must demonstrate left ventricular ejection fraction (LVEF) ≥50% (AHA, 2016)

5.2 Exclusion Criteria

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

1. Current or history of CNS lymphoma

2. Prior exposure to a BTK inhibitor

3. Prior corticosteroids given in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days. Prior chemotherapy, targeted therapy, or radiation therapy

within 3 weeks, antineoplastic therapy with Chinese herbal medicine or antibody based therapies within 4 weeks of the start of study drug.

4. Major surgery within 4 weeks of screening
5. Toxicity recovered to ≤ Grade 1 from prior anti-cancer therapy (except for alopecia, absolute neutrophil count (ANC) and platelets. For ANC and platelets, please follow inclusion criteria #8 [neutrophils] and #9 [platelets])
6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent
7. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (see Appendix 8) or history of myocardial infarction within 6 months of screening
8. QTcF > 480 msecs based on Fridericia's formula or other significant electrocardiogram (ECG) abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block
9. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
10. Active infection systemic including infections requiring oral or IV anti-microbials
11. Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR]).

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-)		HBsAg (+)	
	HBsAg (-) HBcAb (+)	HBV DNA < 1000 IU/mL and anti-viral therapy during study and perform monthly monitoring of HBV DNA	HBsAg(-) HBcAb(+)	HBV DNA>1000 IU/ml
HCV	Antibody (-)			
	Antibody (+)	HCV RNA "Not detected" (<15 IU/mL) Perform monthly monitoring of HCV RNA	Antibody(+)	HCV RNA Detected

12. Pregnant or lactating women
13. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk
14. Requires ongoing treatment with any medication which is a strong or moderate cytochrome P450, family 3, subfamily A (CYP3A) inhibitor or strong CYP3A inducer
15. Known or clinically suspected Richter's transformation at the time of study entry
16. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
17. Has received allogenic hematopoietic stem cell transplantation prior to enrollment

6 STUDY TREATMENTS

6.1 Study Treatment

Subjects will receive BGB-3111 160 mg (two 80 mg white opaque capsules) PO BID. It is recommended that the capsules should be taken approximately 12 hours apart, ± a 2-hour time window. The capsules should be swallowed whole with a glass of water. The capsules should not be chewed, but in case of breakage, additional water should be imbibed to rinse out the mouth.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

The capsule supplies of BGB-3111 will be provided in a child-resistant high density polyethylene (HDPE) bottle with induction seal and bottle label. The label will include at minimum, space to enter the subject number, name of investigator, content and quantity of BGB-3111, protocol number, batch number, bottle number, directions for usage, storage conditions, and precautions.

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

6.2.2 Handling and Storage

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

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

6.2.3 Compliance and Accountability

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

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

6.2.4 Disposal and Destruction

After completion of the study, all unused BGB-3111 will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies will be returned to the sponsor or destroyed on site or depot, after receiving written sponsor approval.

6.3 Subject Numbering and Treatment Assignment

6.3.1 Subject Numbering

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

original screening window. A new informed consent is not required and subject shall maintain the same subject number as originally assigned.

6.3.2 Treatment Assignment

All subjects in the study will receive BGB-3111.

6.3.3 Treatment Blinding

This is an open-label study.

6.4 Dosage and Administration

BGB-3111 will be dispensed by the study center personnel on Day 1 of each cycle (every 4 weeks) during the first year and Day 1 of every other cycle thereafter (every 8 weeks starting on Cycle 13). Subjects will be provided with an adequate supply of study drug for self-administration at home. The investigator should instruct the subject to take the study drug exactly as prescribed. Subjects will be requested to bring their unused medication including empty packaging to the center at each visit. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

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

On the PK blood sampling day, study drug administration will occur at the center under the supervision of the investigator or his/her designee. The investigator or his/her designee must instruct the subject not to self-administer the study drug on those days.

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

6.5 Dose Interruption and Modification

The guidelines set forth in Table 1 should be followed for dose interruption or modification of BGB-3111 for hematologic (Section 6.5.1) and non-hematologic toxicities (other than

hypertension adequately controlled with oral medication or asymptomatic laboratory events; laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) (Section 6.5.2).

Table 1 BGB-3111 Dose Reduction for Toxicity Occurrence

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

Abbreviations: BID, twice a day; QD, daily

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

6.5.1 Dose Reductions for Hematologic Toxicity

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

- Grade 4 neutropenia (lasting >10 days, but if medically indicated, can stop BGB-3111 earlier)
- Grade 4 thrombocytopenia (lasting ≥ 10 days, but if medically indicated, can stop BGB-3111 earlier)
- ≥ Grade 3 neutropenia with fever
- ≥ Grade 3 thrombocytopenia with significant bleeding

Adverse Event	**Severity and Duration**	**Time to Restart**	**Dose Modification**
Absolute neutrophil count decreased	CTCAE Grade 4 ($<0.5x10^9$/L) lasting >10 days	Recover to ANC $>0.75\times10^9$/L	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
Platelet count decreased	CTCAE Grade 4 ($<25x10^9$/L) lasting >10 days	Recover to Platelet $> 50\times10^9$/L	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
Febrile neutropenia	CTCAE Grade 3 (ANC$<1x10^9$/L &	Recover to ANC> 0.75×10^9/L and	Restart at 160mg BID;

	single T>38.3°C, or sustained T>38°C >1hr)	body temperature recovery	For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
	CTCAE Grade 4 (Life-threatening consequences; urgent intervention indicated)	Recover to ANC> 0.75×10^9/L and body temperature recovery	Restart at 160 mg BID; For recurrence: 160 mg BID→80 mg BID →80 mg QD (Table 1)
Thrombocytopenia accompanied by bleeding	CTCAE Grade 3 (Platelets 25-50 x10^9/L) and significant bleeding	Discontinuation	NA
	CTCAE Grade 3 (Platelets <25 x10^9/L) and significant bleeding	Discontinuation	NA

Abbreviations: ANC, absolute neutrophil count; BID, twice a day; CTCAE, Common Terminology Criteria for Adverse Events; hr, hour; NA, not applicable; QD, daily; T. body temperature

Dosing may be restarted at time of recovery of neutrophils ≥ 0.75 x 10^9/L (growth factor support is permitted) or platelets ≥ 50 x 10^9/L. If the same event reoccurs, subjects will restart at one dose level lower. A maximum of 2 dose reductions are allowed.

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

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

6.5.2 Dose Reductions for Non-Hematologic Toxicity

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

dose level-1, per discretion of the treating investigator. BGB-3111 should be permanently discontinued for any intracranial hemorrhage.

6.6 Concomitant Medications and Non-Drug Therapies

6.6.1 Permitted Medications

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

The following treatments are allowed:

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

6.6.1.1 Tumor Lysis Syndrome

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

6.6.2 Prohibited Medications

During study treatment, subjects are prohibited from receiving any anticancer therapy, including but not restricted to chemotherapy, immunotherapy, corticosteroids (at dosages equivalent to >10 mg/day of prednisone), experimental therapy, radiotherapy, and Chinese herbal medications are prohibited. Corticosteroid courses (at dosages equivalent to prednisone >10 mg/day) of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer)

medical condition. Bisphosphonates that have been in steady use for over 3 months are permitted.

6.6.3 Potential Interactions Between the Study Drugs and Concomitant Medications

6.6.3.1 QT-Prolonging Medications

Drugs known to prolong the QT/QTc interval are prohibited, in accordance with FDA Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. A list of drugs with QTc prolongation potential is provided in Appendix 2. If a patient requires treatment with any of these medications on study, and a non-QT-prolonging alternative medication is not available, the medical monitor must be notified. Upon written approval by the medical monitor, treatment with BGB-3111 should be withheld immediately and recommenced to restart study drug at least 5 half-lives following the last use of the QT-prolonging medication.

6.6.3.2 CYP-Inhibiting/Inducing Drugs

Information about clinical drug interactions with BGB-3111 is not available. Based on available nonclinical metabolism data, BGB-3111 is primarily metabolized by CYP3A. Avoid concomitant administration of BGB-3111 with strong CYP3A inhibitors or strong CYP3A inducers (refer to Appendix 5 for a list of these medications). Grapefruit juice and Seville oranges should be avoided, as they may affect the metabolism of BGB-3111. For short-term use (treatment for ≤7 days) of strong CYP3A inhibitors (eg, antifungals and antibiotics), consider interrupting BGB-3111 therapy until the CYP3A inhibitor is no longer needed. The medical monitor should be consulted in these situations.

BGB-3111 is a moderate inhibitor of the human isoenzymes CYP2C8, CYP2C9, and CYP2C19. Drugs that are primarily metabolized by these isoenzymes should be used with caution when administering BGB-3111, with monitoring of drug concentrations as appropriate (refer to Appendix 6 for examples of these medications).

6.7 Discontinuation of Treatment and Premature Withdrawal

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

6.7.1 Discontinuation of Treatment

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

- Death
- Disease progression
- Unacceptable and unmanageable toxicity attributed to BGB-3111
- Pregnancy
- Significant non-compliance of the patient
- Subject misses > 28 consecutive days of dosing

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

Subjects who are discontinued from study drug for any reason (ie, AE or administrative reasons etc.) other than disease progression should not be considered withdrawn from the study. They will continue to be followed for efficacy evaluations per schedule outlined in Table 2 until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them or obtain information by telephone to determine the subject's disease status and survival.

6.7.2 Premature Withdrawal

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

- Subject withdrew consent, permitted at any time during the trial.
- Study Termination by sponsor
- Lost to follow up

If the subject is lost to follow up, investigators should try their best to contact the patient to determine the reason for withdrawal. The information should be recorded in the source document and eCRF.

Subjects may voluntarily withdraw from the study (i.e. withdraw consent) or be withdrawn at the discretion of the investigator at any time. Subjects lost to follow-up should be recorded as such

on the eCRF. For subjects who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject (eg, dates of telephone calls, registered letters).

7 STUDY ASSESSMENTS

7.1 Study Flow and Visit Schedule

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

Table 2 Study Assessments and Procedures Schedule for Study BGB-3111-205

	Pre-treatment	Treatment All cycles are 28 days (4 weeks) in duration				End of Study Assessments		
	Screening / Baseline[1]	Cycle 1	Cycle 2	Cycle 3 – Cycle 13 (every 4 weeks)	Every other cycle (every 8 weeks) starting from second year (C 15, C17, etc.)	EOT[2]	Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (+/-3 days)**	**Day 1 (+/-4 days)**	**Day 1 (+/- 7 days)**	**(within 7 days after stopping treatment)**	**30 days after EOT (+/- 7 days)**	
Visit	0	1	2	3, 4, 5, etc through Cycle 13				
Informed consent	X[3]							
Inclusion/exclusion criteria	X[4]							
Demography	X[5]							
Medical/surgical history/current medical conditions	X[6]							
Diagnosis and extent of cancer	X[7]							
Prior antineoplastic therapy	X							
12-lead ECG[8]	X	X	X			X		
Cardiac ECHO[9]	X							
Lipid panel[10]	X							
ECOG performance status	X	X	X	X	X	X	X	
Height (in cm)	X							
Weight (in kg)	X	X	X	X	X	X	X	
Vital signs and physical examination (including assessment of B symptoms and liver and spleen enlargement)	X[11]	X	X	X	X	X	X	
Hematology[12b]	X	X[12a]	X	X	X	X		

	Pre-treatment	Treatment All cycles are 28 days (4 weeks) in duration				End of Study Assessments		
	Screening / Baseline[1]	Cycle 1	Cycle 2	Cycle 3 – Cycle 13 (every 4 weeks)	Every other cycle (every 8 weeks) starting from second year (C 15, C17, etc.)	EOT[2]	Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (+/-3 days)**	**Day 1 (+/-4 days)**	**Day 1 (+/- 7 days)**	**(within 7 days after stopping treatment)**	**30 days after EOT (+/- 7 days)**	
Chemistry[12c]	X	X[12a]	X	X	X	X		
Coagulation[12d]	X	X[12a]						
Urinalysis (macroscopic; microscopic if required) [12e]	X	X	X	X	X	X		
Serum immunoglobulins and β2-microglobulin [12f]		X	Every 3 cycles (C4, C7, C10, C13)		Every 6 cycles (C19, C25, C31, etc.)			
Direct antiglobulin test (Coombs test)[12g]	X							
Hepatitis B/C testing, HIV testing[12h]	X							
Pregnancy test (if applicable)[12i]	X[11]	X	X	X	X	X		
Study drug administration[13]		X	X	X	X			
Bone marrow biopsy and /aspiration[14]	X	At time of CR, and at time of suspected PD due to progressive cytopenia(s)						
Imaging[15]								
CT scan with contrast of neck, chest, abdomen and pelvis (or MRI)	X	Every 12 weeks during the first 48 weeks, then every 24 weeks						
Brain CT/MRI scan with contrast	X[15]	As clinically indicated						
Concomitant medications	Throughout							
AEs/SAEs	Throughout							
Antineoplastic therapies since discontinuation of study drug							X	X
Survival follow-up[16]								X
	CENTRAL LABORATORY STUDIES							

	Pre-treatment	Treatment All cycles are 28 days (4 weeks) in duration				End of Study Assessments		
	Screening / Baseline[1]	Cycle 1	Cycle 2	Cycle 3 – Cycle 13 (every 4 weeks)	Every other cycle (every 8 weeks) starting from second year (C 15, C17, etc.)	EOT[2]	Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (+/-3 days)**	**Day 1 (+/-4 days)**	**Day 1 (+/- 7 days)**	**(within 7 days after stopping treatment)**	**30 days after EOT (+/- 7 days)**	
CCI								
CCI								

Abbreviations: AEs, adverse events; C, cycle; CR, complete response; CT, computed tomography; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FISH, fluorescence in situ hybridization; HIV, human immunodeficiency virus; CCI magnetic resonance imaging; SAEs, serious adverse events; CCI X, to be performed

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

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

1. Screening evaluations will be performed and completed within 28 days prior to the first dose of BGB-3111. Bone marrow assessment is allowed to be conducted within 60 days prior to the first dose of BGB-3111. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Cycle 1 Day 1.
2. If at any time the subject relapses, 10 ml blood must be collected within 7 days for drug resistance studies.

3. Written informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
4. The investigator will review and ensure that the subject meets all of the inclusion and none of the exclusion criteria.
5. Demography includes gender, and date of birth (or age).
6. Relevant medical history (ie. previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility, and current medical conditions.
7. Diagnosis and extent of cancer. Other background information including history of disease and current disease status, staging, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.
8. Perform a 12-lead ECG in triplicate at screening and EOT. For subjects with PK sample collection, a 12-lead ECG in triplicate will also be performed pre-dose (within 30 min of dose) and 2 hours (+/- 30 min) post-dose on Cycle 1 Day 1 and Cycle 2 Day 1. Subjects should be in the semi-recumbent or supine position
9. Cardiac ECHO to evaluate cardiac function; left ventricular ejection fraction must be ≥50%, investigation up to 30 days before enrollment acceptable.
10. Lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides performed at screening only.
11. A complete or targeted physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified. Complete physical exam includes assessments of cardiovascular, respiratory, abdominal, and neurological systems as well as lymph nodes /spleen, skin, oropharynx, and extremities. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. Clinical suspicion of disease progression at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats. If the physical examination is not completed +/- 7 days of the radiological tumor assessment, a separate physical examination should be performed.
12. Laboratory assessments include the following:
    a. Screening labs performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.
    b. Hematology, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, blasts) and platelet count. In the event of neutropenia (absolute neutrophil count < 0.75 x 10^9/L) or thrombocytopenia (platelets of less than 50 x 10^9/L), these assessments will be conducted as frequently as the investigator feels it necessary and until

toxicity resolves to ≤ Grade 2 or baseline (ANC ≥0.75x10^9/L).

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

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

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

f. Serum immunoglobulins (i.e., IgG, IgM, IgA) and β2-microglobulin will be measured pre-dose on Cycle 1 Day 1 and Day 1 of every 3 cycles for the first 52 weeks (C4, C7, C10, C13), then every 6 cycles thereafter during the treatment period. Beta-2 microglobulin test will be conducted only when sites have the capability.

g. Coombs test will be performed at screening.

h. Hepatitis B/C serologic markers and viral load will be tested. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by PCR if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes Hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. See Section 7.4.4.9 for more information.

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

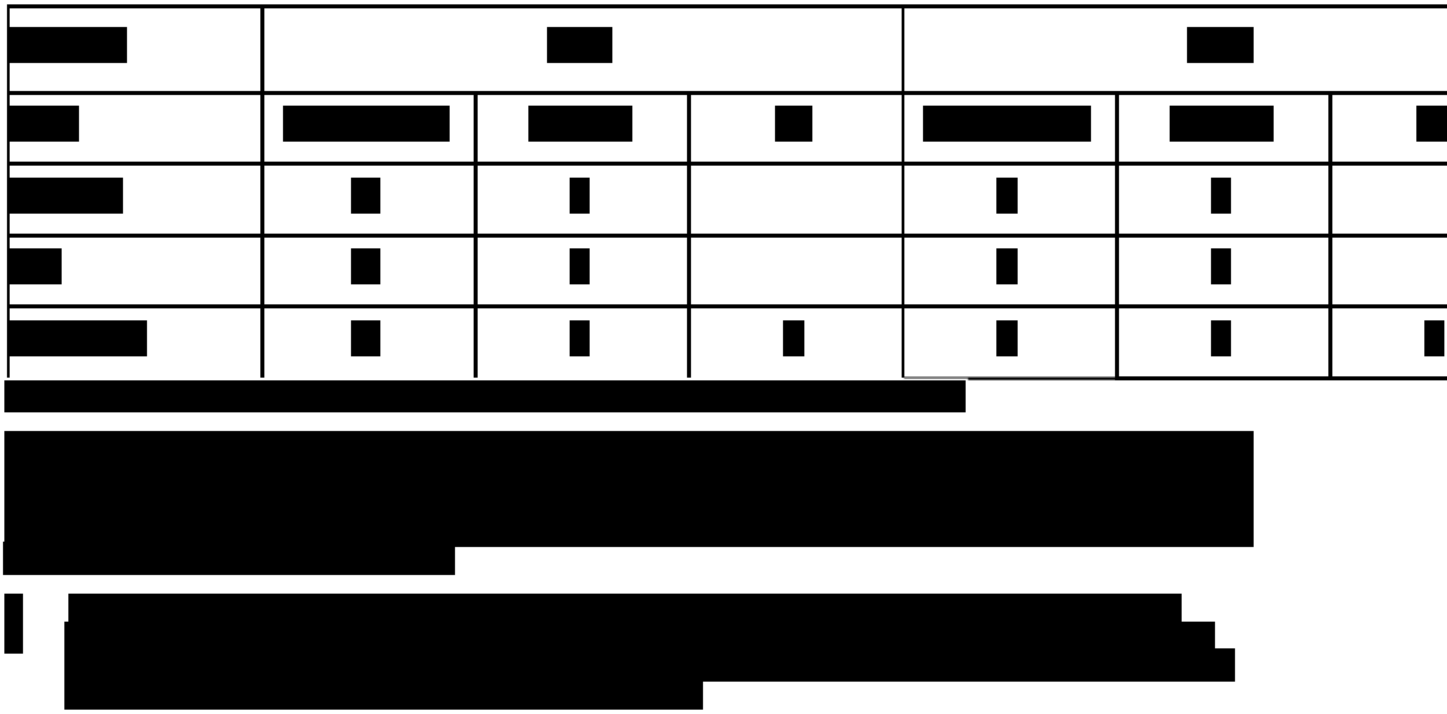
13. Subjects will receive BGB-3111 at a dosage of 160 mg (2 80 mg white opaque capsules) PO BID (subjects will be required to fast for at least 2 hours before and 1 hour after each administration throughout the study). BGB-3111 will be administered on a 28-day cycle and will continue for until disease progression, unacceptable toxicity, death, withdrawal of consent, end of study, or discontinuation from the study for any reason. All subjects will have an EOT visit within 7 days after stopping study drug. All subjects will have a follow-up visit 30 ± 7 days after the last dose of the study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.

14. A bone marrow aspiration and biopsy (smear and IHC) will be performed at screening for all subjects. Bone marrow assessment is allowed to be conducted within 60 days prior to the first dose of BGB-3111. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a

possible CR (eg, physical exam or CT scan indicating a possible CR), a bone marrow aspiration and biopsy will be obtained to confirm the CR.

15. CT scans must encompass neck, chest, abdomen, and pelvis and include oral and IV contrast. A brain scan is required if clinically indicated. In all case, an MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study. See Appendix 3 (CLL) and Appendix 4 (SLL) for tumor response. Tumor assessment by CT or scan will occur every 12 weeks during the first 52 weeks, and then every 24 weeks until disease progression or end of study, whichever comes first. CT scan is allowed to be conducted within 30 days prior to the first dose of BGB-3111. In subjects with bone marrow tumor involvement prior to study drug, CR should be confirmed by bone marrow biopsy. Unscheduled response assessments may be performed based on physical examination or laboratory findings, at the discretion of the investigator. Clinical suspicion of disease progression at any time will require radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.
16. Survival information will be collected via telephone call every 3 months.
17. CCI [redacted]

Table 3 CCI



7.2 Subject Demographics/Other Baseline Characteristics

7.2.1 Demography

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

7.2.2 Medical History

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

7.2.3 Other Baseline Characteristics

Other background information including history of disease and current disease status, Rai and Binet staging at diagnosis and screening, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.

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

A CT scan may be conducted within 30 days prior to the first dose of BGB-3111.

For further details on eligibility assessments, please see Table 2.

7.2.3.1 The Modified Rai classification

Three prognostic groups are defined by the modified Rai classification (Rai, 1987).

- Low-risk disease defined as patients who have lymphocytosis with leukemia cells in the blood and/or marrow (lymphoid cells >30%; formerly considered Rai stage 0)
- Intermediate-risk disease defined as patients with lymphocytosis, enlarged nodes in any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not) (formerly considered Rai stage I or stage II)
- High-risk disease includes patients with disease-related anemia (as defined by a Hb level <110 g/L [11 g/dL]; formerly stage III) or thrombocytopenia (as defined by a platelet count<100 x 10^9/L; formerly stage IV)

7.2.3.2 Binet Staging System (Binet 1981)

Staging is based on the number of involved areas, as defined by the presence of enlarged lymph nodes of greater than 1 cm in diameter or organomegaly, and on whether there is anemia or thrombocytopenia (Binet et al, 1981).

Areas of involvement considered for staging

1. Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged)

2. Axillae (involvement of both axillae counts as one area)

3. Groins, including superficial femorals (involvement of both groins counts as one area).

4. Palpable spleen

5. Palpable liver (clinically enlarged)

Stage A. Hb ≥ 100 g/L (10 g/dL) and platelets ≥ 100 x 10^9/L and up to 2 of the above involved

Stage B. Hb ≥ 100 g/L (10 g/dL) and platelets ≥ 100 x 10^9/L and organomegaly greater than that defined for stage A (ie, ≥ 3 areas of nodal or organ enlargement)

Stage C. Hb < 100 g/L (10 g/dL) and/or a platelet count < 100 x 10^9/L, irrespective of organomegaly

7.2.3.3 Revised Ann Arbor Staging System

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

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

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

(Lister et al, 1989; Cheson et al, 2014)

7.3 Efficacy

Response will be evaluated by IRC review in accordance with the modified 2008 International Working Group on CLL Guidelines for subjects with CLL (Appendix 3) and the Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Appendix 4).

Clinical evaluation and tumor assessments will be performed, as is indicated in Table 2, based on physical examination, laboratory evaluation, radiological assessment and bone marrow biopsy (to confirm complete responses in subjects with bone marrow tumor involvement prior to study drug).

Clinical suspicion of disease progression at any time will require a physical examination, laboratory evaluation, and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent radiological assessments must be performed according to the originally planned schedule from baseline (ie, every 12 weeks from baseline during the first year and every 24 weeks thereafter).

Complete response should be confirmed by contrast CT. In subjects with bone marrow tumor involvement prior to study drug, CR should be confirmed by bone marrow biopsy.

7.3.1 Definition of Response (CLL)

7.3.1.1 Complete Remission (CR)

CR requires all of the following criteria to be met:

- Peripheral blood lymphocytes (evaluated by blood and differential count) < 4 x 10^9/L (4000/μL)
- Absence of significant lymphadenopathy (eg, lymph nodes > 1.5 cm in diameter) by CT scan
- No hepatomegaly or splenomegaly by CT scan
- Absence of constitutional symptoms and extralymphatic site of disease
- Blood counts above the following values:
    - Neutrophils >1.5 x 10^9/L without need for exogenous growth factors
    - Platelets >100 x 10^9/L without need for exogenous growth factors
    - Hemoglobin >110 g/L without red blood cell transfusion or need for exogenous erythropoietin
- Bone marrow aspirate and biopsy should be performed within 4 weeks of clinical signs/symptoms to demonstrate CR. To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

7.3.1.2 CR with Incomplete Bone Marrow Recovery (CRi)

Fulfills all requirements for CR except with CRi has persistent neutropenia, anemia, or thrombocytopenia thought to be unrelated to the disease and likely related to drug toxicity, and has a hypocellular bone marrow. The bone marrow aspirate and biopsy must have less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

7.3.1.3 Nodular Partial Response (nPR)

Fulfills all requirements for CR except in nPR, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as “nodular PR.” Moreover, IHC should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. A marrow biopsy should be compared with that of pretreatment marrow.

7.3.1.4 Partial Remission (PR)

Partial remission (partial response) is described by the criteria below and is fully defined in Appendix 3. A PR requires improvement in at least two group A criteria (lymphadenopathy, hepatomegaly, splenomegaly, blood lymphocytes, bone marrow lymphocytes) and at least one group B criterion (platelet count, Hb, neutrophils). For a subject having only one Group A abnormality at baseline, meeting the PR criteria for that one parameter is sufficient to meet PR requirements as long as at least one Group B criterion is also met.

Group A

- A decrease in the number of blood lymphocytes by 50% or more from baseline
- Reduction in lymphadenopathy by CT scans as defined by the following:
    - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes
    - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm) one must have a 0.5 cm increase to be considered PD.
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan
- The blood count should show one at least one of the following results:
    - Neutrophils >1.5 × 10^9/L without need for exogenous growth factors
    - Platelet counts >100 × 10^9/L or 50% improvement over baseline without need for exogenous growth factors
    - Hemoglobin >110 g/L or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin
- The bone marrow must show 50% reduction in the marrow infiltrate or in the B-lymphoid nodules

NOTE: Constitutional symptoms persisting for more than 1 month should be recorded.

7.3.1.5 Partial Remission with lymphocytosis (PR-L)

Subject has lymphocytosis (either an increase from baseline, or less than 50% decrease from baseline) and meets at least one category A and one category B criterion.

7.3.1.6 Stable Disease (SD)

Subject has not achieved a PR-L, PR, nPR, CRi, or CR and does not have confirmed PD.

7.3.1.7 Progressive Disease (PD)

Progressive disease during or after therapy is characterized by at least one of the following:

- Lymphadenopathy: disease progression occurs if one of the following events is observed:
    - Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates
    - An increase by 50% or more in greatest determined diameter of any previous site, minimum 0.5 cm if nodes <2 cm
    - An increase from the nadir by ≥ 50% in SPD of multiple targeted lesions
- Non-target lesion: unequivocal increase in the size of one or more nodal or extranodal non-target lesions.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly
- Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy (type of transformation, presence of Epstein-Barr virus [if Hodgkins])
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL
    - During therapy:

    Cytopenias may occur as a side effect of many therapies and should be assessed according CTCAE v.4.03. During therapy, cytopenias cannot be used to define disease progression unless a concurrent bone marrow examination confirms that cytopenia is not due to a treatment effect.

    - After treatment:

    The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. Bone marrow aspiration and biopsy must be performed to confirm PD by cytopenias alone.

7.3.1.8 Lymphocytosis

In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD. Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop other definitive signs of PD (ie, at least one feature suggesting worsening CLL other than lymphocytosis [eg, anemia, thrombocytopenia, lymphadenopathy, or hepatosplenomegaly]) or the occurrence of another reason to discontinue therapy. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening disease should also not be considered definitive evidence of PD until other potential causes are ruled out. Progressive disease must be considered unequivocal. If PD is suspected, clinical examination, CT, and peripheral blood counts should be obtained, and a bone marrow biopsy considered, to provide objective assessment of CLL status. Similarly, persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis as described above.

7.3.2 Definition of Response (SLL)

Efficacy assessments of SLL will use the applicable Lugano response criteria (as shown in Appendix 4), with CT scans after weeks 12, 24, 36 and 48, then every 48 weeks until disease progression or end of study, whichever comes first. A bone marrow biopsy and aspirate is required at the time of CR (if the patient attains criteria for complete remission in every other respect) and at the time of suspected cytopenic progression.

7.3.3 Physical Examination (Constitutional Symptoms, Organ Examination)

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

7.3.4 Radiological Tumor Assessment

All subjects must have CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites. CT of the brain is only indicated if clinical findings or symptoms suggest CNS involvement.

The CT scan will be repeated every 12 weeks during the first 48 weeks and every 24 weeks thereafter until documented disease progression according to the 2014 International Working Group in NHL criteria (Appendix 4). Subjects will be treated by the investigator according to the local radiologist's assessments.

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

A CT of the brain is only indicated if clinical findings or symptoms suggest CNS involvement.

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

7.3.5 Bone Marrow Assessment

A unilateral bone marrow aspirate and biopsy must be performed at screening within 60 days of the first dose for all subjects, provided there has been no intervening therapy between the time of the biopsy and start of study drug. In those subjects who had evidence of bone marrow disease at screening, upon achieving a possible CR (eg, physical exam or CT scan indicating a possible CR), a bone marrow aspirate and biopsy should be obtained to confirm the CR.

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

7.3.6 Missed evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible unless it is too close in time to the next scheduled evaluation.

7.4 Safety

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

7.4.1 Adverse Events

All adverse events, including SAEs, will be collected as described in Section 9.2.2. The accepted regulatory definition for an AE is provided in Section 9.1. Important additional requirement for reporting SAEs are explained in Section 9.2. Asymptomatic lymphocytosis should not be regarded as an AE and reported.

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of 50% compared to baseline and ≥5,000/μL that occurs in the setting of improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hb or platelet count), or disease-related symptoms. Given the known mechanism of action of BCR-inhibiting agents including BGB-3111, treatment-related lymphocytosis is an expected and frequent pharmacodynamics phenomenon observed with initiation (or re-initiation) of BGB-3111. In this study, asymptomatic treatment-related lymphocytosis should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

7.4.2 Physical Examination, Vital Signs, Height, and Weight

A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), weight, and constitutional symptoms examination will be performed at each study visit. Height (cm) is determined at screening/baseline only.

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

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

7.4.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, each visit during study treatment, and at EOT Visits. Appendix 7 will be used to assess performance status.

7.4.4 Laboratory Evaluations

Laboratory assessments should be performed at a local certified laboratory. Clinical chemistry, hematology, coagulation, urinalysis, serum immunoglobulins, and direct antiglobulin test (Coombs test), immunophenotyping will be performed at the time points specified in Table 2 and may also be performed as medically necessary. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and urine tests were performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

7.4.4.1 Hematology

Hematology evaluation includes Hb, hematocrit, platelet, red blood cell, white blood cell (WBC) and differential count, including neutrophils (bands included), lymphocytes, monocytes, eosinophils, basophils, immature cells. If there is neutropenia (<0.75 x 10^9/L) or thrombocytopenia (platelet count < 50 x 10^9/L), more frequent evaluation of these cell counts can be determined by investigators, until toxicity is ≤Grade 2.

7.4.4.2 Clinical Chemistry

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

7.4.4.3 Serum Lipid Profile

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

7.4.4.4 Coagulation

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

7.4.4.5 Urinalysis with Dipstick

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and

specific gravity. If urine protein is ≥2+ by dipstick, a 24-hour urine for total protein will be obtained and evaluated.

7.4.4.6 Serum Immunoglobulin and β2microglobulin

Serum immunoglobulin (IgG, IgM, IgA) and β2 microglobulin (if applicable) will be measured pre-dose on Cycle 1 Day 1 (C1D1), every 3 cycles (C4D1, C7D1, C10D1, C13D1), and then every 6 cycles (C19D1, C25D1, C31D1 and so on) thereafter. Beta-2 microglobulin will be conducted in the sites with the capability.

7.4.4.7 Direct Antiglobulin Test (Coombs test)

Direct antiglobulin test will be measured at screening.

7.4.4.8 Pregnancy test

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

7.4.4.9 Hepatitis B/C Testing

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

Subjects positive for HCV antibody, but negative for HCV RNA (≤15 IU/mL), must undergo monthly HCV RNA screening. Subjects with known HIV are excluded from the study. Subjects

with detected HCV RNA should stop study drug and antiviral therapy should be initiated. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 4 below shows how the results for HBV/HCV and HBV/HCV testing at screening relate to the inclusion and exclusion criteria.

Table 4 Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by PCR)

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA < 1000 IU/mL and anti-viral therapy during study and perform monthly monitoring of HBV DNA*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA > 1000 IU/mL*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not detected" (<15 IU/mL)* *Perform monthly monitoring of HCV RNA*	**Antibody (+)** *HCV RNA Detected*

Abbreviations: HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus

7.4.5 Electrocardiogram

Perform a 12-lead ECG in triplicate at screening and EOT. For subjects with PK sample collection, a 12-lead ECG in triplicate will also be performed pre-dose (within 30 min of dose) and 2 hours (± 30 min) post-dose on Cycle 1 Day 1and Cycle 2 Day 1. Subjects should be in the semi-recumbent or supine position.

7.4.6 CCI

[redacted]

CCI [redacted]

[redacted]

7.5 CCI [redacted]

[redacted]

- [redacted]
- [redacted]

7.6 Appropriateness of Measurements

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

8 DATA HANDLING AND QUALITY ASSURANCE

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

8.1 Data Collection

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

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

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

Missing Data Handling: No imputation of values for missing data will be performed, except for missing or partial start and end dates for adverse events and concomitant medications, will be imputed according to pre-specified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

8.2 Data Management/Coding

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

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®; http://www.meddra.org/how-to-use/support-documentation/english) version 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) http://www.who.int/hiv/topics/pharmacovigilance/3_who_drug_dictionary.pdf. Concomitant diseases/medical history will be coded using the MedDRA Version 18.1 or higher.

8.3 Quality Assurance

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

9 SAFETY MONITORING AND REPORTING

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

9.1 Adverse Events

9.1.1 Definitions and Reporting

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

Examples of an AE include:

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

Examples of an AE do not include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory results and diagnostics reports) relative

to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the appropriate AE or SAE eCRF pages. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

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

9.1.1.1 Assessment of Severity

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

9.1.1.2 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 IB and/or Product Information, for marketed products, in the determination of his/her assessment.

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

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions:

- Definitely related: There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (When necessary the

positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment.

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

The causality for cases assessed with 5-point scale will be mapped to 2-point scale during aggregate safety data analysis according to the BeiGene latest mapping rule.

9.1.1.3 Follow-Up of Adverse Events and Serious Adverse Events

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

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

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be resent to the sponsor within the time frames outlined in Section 9.3.1.

9.1.2 Laboratory Test Abnormalities

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

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

9.2 Serious Adverse Events

9.2.1 Definitions

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

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

- Results in disability/incapacity

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

- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

9.2.2.1 Adverse Event Reporting Period

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

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

Table 5 Timeframe for Reporting Serious Adverse Events to the Sponsor

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

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

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

9.2.2.2 Completion and Transmission of the Serious Adverse Event Report

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

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the SAE and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.1.2.

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

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

9.2.2.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.2.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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

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

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

9.2.2.4 Serious Adverse Events Related to Study Participation

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

9.3 Pregnancy Reporting

A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study. All post-study assessments will be collected at the time of discontinuation as described in Table 2.

If a female subject or the partner of a male subject becomes pregnant while receiving investigational therapy or within 90 days for BGB-3111 after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the sponsor within 2 weeks of learning of a subject's or male subject's female partner's pregnancy. The subject or male subject's female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE, as described in Section 9.1 and Section 9.2 and will be followed as described in Section 9.1.1.3.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.2.2.1. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study drug by the investigator, will be reported to the sponsor as described in Section 9.2.2.2. While the investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

9.4 Lack of Efficacy

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

9.5 Safety Monitoring Committee

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

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

A Safety Monitoring Committee (SMC) will monitor safety data periodically throughout the study. As the efficacy endpoints require longer length of follow-up to be adequately evaluated, a formal interim review of data collected during the study by the SMC will focus on the safety aspects of the study. This early safety review will occur 3 months after enrollment of the 25th subject or at 6 months after the first subject is enrolled, whichever comes first. No recruitment stop is planned for this interim safety review. Subsequent safety data review is outlined in SMC charter. In the case of major toxicity or efficacy concerns, the SMC can recommend to modify the trial conduct.

10 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

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

10.1 Primary, Secondary and CCI Study Endpoints

10.1.1 Primary Endpoint

The primary endpoint of the study is the overall response rate, as determined by IRC, defined as the achievement of PR, including nPR, PR-L, CR, or CRi according to modified IWCLL Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013; see Appendix 3) and the

Revised Criteria for Response for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014; see Appendix 4).

10.1.2 Secondary Endpoints

Efficacy (using response assessment as determined by IRC):

- Progression-free survival, time from treatment initiation to first documentation of progression by IWCLL criteria for response for malignant lymphoma or death, whichever is earlier
- Duration of response, time from the first response documentation according to above response criteria to the date that PD is objectively documented or death, whichever is earlier
- Time to response, time from treatment initiation to first signs of response
- ORR by investigator: overall response rate as determined by investigator

Safety:

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

10.1.3 CCI

[redacted]

10.2 Statistical Analysis

10.2.1 Analysis Populations

The Safety Population includes all subjects who received any dose of BGB-3111. It will be the primary population for the efficacy and safety analyses.

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

The PK Population includes all subjects for whom valid BGB-3111 PK parameters can be estimated.

10.2.2 Subject Disposition

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

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

10.2.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial diagnosis; categorical variables include sex, age group (<65 vs. ≥65), disease stage, ECOG-PS, prior line(s) of therapy for CLL, del(17p), del(11q), baseline Rai Stage, Bulky disease (LDi<5 cm vs. ≥5 cm), cytopenias (yes vs. no), β2-microglobulin (≤3 mg/L vs >3 mg/L).

10.2.4 Prior and Concomitant Therapy

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

10.2.5 Efficacy Analyses

10.2.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is overall response rate according to modified IWCLL criteria (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013) and 2014 Revision for Malignant Lymphoma in subjects with SLL (Cheson et al, 2014), as assessed by IRC.

The overall response rate (ORR) is defined as the proportion of subjects achieving a best overall response (BOR) of CR, CRi, nPR, PR or PR-L for CLL patients, and CR, PR for SLL patients, per the IRC prior to initiation of subsequent antineoplastic therapy.

In this population, the ORR in the historical control is assumed to be approximately 32% based on recent trials. The ORR in this study is estimated as 63%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: ORR=32%

Ha: ORR >32%

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

Clopper-Pearson 2-sided 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate.

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

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

Sensitivity analyses will be performed for the primary endpoint in the PP Population.

10.2.5.2 Secondary Efficacy Analysis

Progression-free survival is defined as the time from the starting date of BGB-3111 to the date of first documentation of disease progression or death, whichever occurs first.

Kaplan-Meier (KM) method will be used to estimate progression event-free curves and corresponding quantiles (including the median). A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982). The PFS rate at 12 months, defined as the percentages of subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926).

The PFS censoring rule will follow 国家食品药品监督管理局《抗肿瘤药物临床试验终点技术指导原则》（2012）.

The DOR is defined as the time from the date that the response criteria (CR, CRi, nPR, PR, or PR-L) are first met to the date that PD is objectively documented or death, whichever occurs first. Subjects who do not have disease progression will be censored at their last valid assessment. The TTR is defined as time from the starting date of BGB-3111 to the date the response criteria are first met. The DOR will be similarly analyzed using the KM method as described above. The KM estimates of DOR will be plotted over time. The TTR will be summarized by sample statistics such as sample mean, median, and standard deviation.

Disease-related symptoms including weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly, and anorexia. Percentage of subjects improving from baseline by at least 1 grade for 2 consecutive assessments prior to initiation of subsequent antineoplastic therapy will be provided.

The ORR is defined as the proportion of subjects achieving a best overall response (BOR) of CR, CRi, nPR, PR or PR-L for CLL patients, and CR, PR for SLL patients, per the investigator prior to initiation of subsequent antineoplastic therapy.

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

10.2.5.3 CCI

[redacted]

10.2.5.4 Subgroup Analysis

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: sex, age group (<65 vs. ≥65) disease stage, ECOG-PS, prior line of therapy for CLL, CCI baseline Rai Stage, bulky disease (LDi<5 cm vs. ≥5 cm), cytopenias (yes vs. no), β2-microglobulin (≤3 mg/L, vs. >3 mg/L). Within group values (rates or means/medians) will be presented in forest plots.

10.2.6 CCI

[redacted]

10.2.7 CCI

[redacted]

10.3 Safety Analyses

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

10.3.1 Extent of Exposure

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

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

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

10.3.2 Adverse Events

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

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

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

10.3.3 Laboratory Analyses

Clinical laboratory (ie, hematology, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous

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

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

10.3.4 Vital Signs

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

10.3.5 Electrocardiogram

Electrocardiogram assessments will be performed at the screening visit, pre-dose (within 30 min of dose) and 2 hour (+/- 30 min) post-dose on Cycle 1 Day 1 and EOT. Descriptive statistics for ECG parameters will be presented.

10.4 Sample Size Consideration

Approximately 80 subjects will be enrolled.

The sample size calculation was based on the level of precision of the estimated ORR and power of its comparison to the historical rate. Assuming ORR of 63% in the trial as compared to 32% in the historical control, using a binomial exact text, the power is >0.99 with 80 subjects to demonstrate statistical significance at a 1-sided alpha of 0.025. For an observed ORR of 63%, the 95% exact CI is (51.5%, 73.5%).

10.5 Interim Analysis

No interim analysis is planned in this study.

10.6 Other Statistical Issues

Primary, secondary, and CCI endpoints will be summarized in the Safety Population.

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

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

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory Authority Approval

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

11.2 Investigator Responsibilities

11.2.1 Good Clinical Practice

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

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

11.2.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, 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 subjects (eg, advertisements or information that supports or supplements the informed

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

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

11.2.3 Informed Consent

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

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

11.2.4 Investigator Reporting Requirements

As indicated in Section 9.1, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at

his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5 Confidentiality

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

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

11.2.6 Case Report Forms

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

11.2.7 Drug Accountability

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

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

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

11.2.8 Inspections

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

11.2.9 Protocol Compliance

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

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

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

11.3.2 Study Report and Publications

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

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

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

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

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

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

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

11.4 Study and Study Center Closure

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

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

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but

not limited to, safety or ethical issues or severe non-compliance. 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. In addition, if BGB-3111 becomes commercially available, the sponsor may transition patients from study treatment to commercial drug supply.

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

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

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

11.5 Records Retention and Study Files

11.5.1 Study Files and Retention of Records

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

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

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

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

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

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

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

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

11.6 Provision of Study Results and Information to Investigators

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

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

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

11.7 Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

11.8 Joint Investigator/Sponsor Responsibilities

11.8.1 Access to Information for Monitoring

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

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

11.8.2 Access to Information for Auditing or Inspections

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

12 REFERENCES

Bachow SH, et al. Evolving Strategies for the Treatment of Chronic Lymphocytic Leukemia in the Upfront Setting. CurrHematol Malig Rep. 2016;11(1):61-70.

Badoux XC, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood. 2011;117(11):3016-24.

BeiGene Investigator's Brochure, BGB-3111. Edition 4, February 2017.

Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48:198-204.

Boggs DR, et al. Am J Hematol. 1987;25(3):349-54.

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Burger JA, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373(25):2425-37.

Byrd JC, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369(1):32-42

Byrd JC, et al., Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N. Engl. J. Med 2014; 371(93): 213-23.

Chang BY, et al., Egress of CD19+CD5+ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. Blood 2013;122(14): 2412-2424.

Chen W, et al., Cancer statistics in China 2015. CA Cancer J Clin. 2016 66(2): 115-132.

Cheson BD, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014;32:3059-3068.

Cheson BD, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol. 2012;30(23):2820-2.

Common Terminology Criteria for Adverse Events, Version 4.03.Cancer Therapy Evaluation Program.14 June 2010.

Cramer P, et al. Outcome of advanced chronic lymphocytic leukemia following different first-line and relapse therapies: a meta-analysis of five prospective trials by the German CLL Study Group (GCLLSG). Haematologica 2015;100(11):1451-9.

de Claro RA, et al. FDA Approval: Ibrutinib for patients with previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia. Clin Cancer Res. 2015;21(16):3586-90.

Else M, et al. The long-term outcome of patients in the LRF CLL4 trial: the effect of salvage treatment and biological markers in those surviving 10 years. Br J Haematol. 2016;172(2):228-37.

Food and Drug Administration Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf

Food and Drug Administration Guidance for Industry:E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf.

Furman RR, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;13;370(11):997-1007.

Goede V, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(12):1101-10.

Greenwood, M. The natural duration of cancer. Reports of Public Health and Related Subjects, HMSO, London, 33:1-26.1926.

Hallek M, et al. Clarification of IWCLL criteria for a partial response to therapy. 2013; e letter, published November 13, 2013. http://www.bloodjournal.org/content/111/12/5446/tab-e-letters#clarification-of-iwcll-criteria-for-a-partial-response-to-therapy

Hallek M, et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. 2012; e letter, published June 4, 2012. http://www.bloodjournal.org/content/early/2008/01/23/blood-2007-06-093906/tab-e-letters?sso-checked=true?sso-checked=true#response-assessment-in-chronic-lymphocytic-leukemia-treated-with-novel-agents-causing-an-increase-of-peripheral-blood-lymphocytes

Hallek, M, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.

Hillmen P, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2008;25(35):5616-23.

International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17(6):779-90.

Jain N, et al. Initial treatment of CLL: integrating biology and functional status. Blood. 2015;126(4): 463-70.

Keating MJ, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23(18):4079-88.

Knauf WU, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(26): 4378-84.

Lister TA, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7(11):1630-6.

Lymphoma Information Network. http://www.lymphomainfo.net/lymphoma.html.

Maddocks KJ, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol. 2015;1(1):80-7.

Oken MM, et al .Toxicity and Response Criteria of The Eastern Cooperative Oncology Group.Am J Clin Oncol 1982;5:649-655.

Rai KR. A critical analysis of staging in CLL. In: Gale RP, Rai KR, eds. Chronic Lymphocytic Leukemia: Recent Progress and Future Directions. New York, NY: Liss; 1987:253-264.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.

Sorensen JM, et al. Treatment of refractory chronic lymphocytic leukemia with fludarabine phosphate via the group C protocol mechanism of the National Cancer Institute: five-year follow-up report. J Clin Oncol. 1997;15(2):458-65.

Stadler N, et al. A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia. Adv Ther. 2016;33(10):1814-1830.

Stilgenbauer S, et al. Management of chronic lymphocytic leukemia. Am Soc Clin Oncol Educ Book. 2015:164-75.

Tam C, et al.The BTK inhibitor, BGB-3111, is safe, tolerable, and highly active in patients with relapsed/ refractory b-cell malignancies:initial report of a phase 1 first-in-human trial.2015 American Society of Hematology (ASH).

Vollbrecht C, et al. Comprehensive analysis of disease-related genes in chronic lymphocytic leukemia by multiplex PCR-based next generation sequencing. Plos One. 2015;10(6):e0129544.

Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood. 2014;123(12):1810-7.

Yang C, et al. Incidence survey of leukemia in China. Chin Med Sci J. 1991;6(2):65-70.

李小秋. 中国淋巴瘤亚型分布：国内多中心性病例 10002 例分析. 诊断学理论与实践第 11 卷第 II 期：111-115.

国家食品药品监督管理局《抗肿瘤药物临床试验终点技术指导原则》（2012）.

13 APPENDICES

Appendix 1 Signature of Investigator

PROTOCOL TITLE: A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

PROTOCOL NO: BGB-3111-205

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Appendix 2 Medications Which are Known toProlong the QT Interval and/or Induce Torsades de Pointes to be Avoided

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

Antilipemic probucol
Antidpressants citalopram
Opiate agonists levomethadyl methadone
Gastrointestinal stimulant cisapride

Appendix 3 CLL Response Definitions

Parameter	CR/CRi*	PR/nPR*	PR With Lymphocytosis	Progressive Disease*
Group A				
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%[b]	Decrease ≥ 50%	Increase ≥ 50% or new lesion[c]
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. **Hypocellular marrow defines CRi.**	50% reduction in marrow infiltrate, or B-lymphoid nodules. **Nodular PR (nPR): criteria for CR are met in setting of B-lymphoid nodules/B-cell clusters.**	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/μL[a]	> 100,000/μL or increase ≥ 50% over baseline[a]	> 100,000/μL or increase ≥ 50% over baseline[a]	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL[a]	> 11 g/dL or increase ≥ 50% over baseline[a]	> 11 g/dL or increase ≥ 50% over baseline[a]	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL[a]	> 1,500/μL or > 50% improvement over baseline[a]	> 1,500/μL or > 50% improvement over baseline[a]	

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete remission (response); CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PD, disease progression; PR, partial remission (response); SD, stable disease.
Continued on next page.

Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

CR*: all of the criteria have to be met, and patients must lack disease-related constitutional symptoms and extralymphatic site of disease.
PR*: at least two of the criteria of group A (lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes) plus one of the criteria of Group B (platelets, hemoglobin, or neutrophils) have to be met.

NOTE: Patients with only one abnormality in Group A at baseline are still assessable for PR. The one Group A parameter must be met (and the other two must still be normal), and at least one Group B criteria must be met (Hallek et al, 2013).
Partial response with lymphocytosis*: presence of lymphocytosis, plus ≥50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the Group B criteria must be met (Hallek et al, 2012);
SD: is absence of progressive disease and failure to achieve at least a PR.
PD* progressive disease: at least one of the above progressive disease criteria has to be met. Transformation to a more aggressive histology (eg, Richter's Syndrome) meets the definition of PD.

NOTE: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic (Hallek et al, 2012).
† Sum of the products (SPD) of multiple lymph nodes (as evaluated by CT scans, or by physical examination).
‡ These parameters are irrelevant for some response categories

a. Without need for exogenous growth factors
b. In the sum products of ≤6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes
c. An increase of 50% or more in greatest determined diameter of any previous site, minimum 0.5 cm if nodes <2 cm in a single lymph node defines PD. An increase from the nadir by ≥ 50% in SPD of multiple targeted lesions. An unequivocal increase in the size of one or more nodal or extranodal non-target lesions.

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

BTK inhibition may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. The opposite may occur during periods of temporary holds of BTK inhibitors (due to adverse events or other reasons), and leukemia cells may redistribute from the blood to lymphoid tissue; this also is not a sign of treatment failure or progressive disease.

Isolated increase in lymph nodes and/or splenomegaly during periods of BGB-3111 hold will not be considered as progressive disease unless confirmed by a repeat imaging studies at least 6 weeks after restarting study drug administration. The response category "indeterminate due to BGB-3111 hold" should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

Appendix 4 SLL Response Definitions

Response assessment criteria for SLL (Cheson et al, 2014**)**

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

Computer tomography (CT) is preferred for low or variable FDG avidity.

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

Response and site	CT-Based Response
Complete	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Absent
Organ enlargement	Regress to normal
New lesions	None
Bone marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Absent/normal, regressed, but no increase
Organ enlargement	Spleen must have regressed by >50% in length beyond normal
New lesions	None
Bone marrow	Not applicable

Continued on next page.

No response or stable disease	Stable disease
Target nodes/nodal masses, extranodal lesions	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	No increase consistent with progression
Organ enlargement	No increase consistent with progression
New lesions	None
Bone marrow	Not applicable
Progressive disease	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	PPD progression: An individual node/lesion must be abnormal with: LDi > 1,5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions> 2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If not prior splenomegaly, must increase by at least 2 cm from baseline
	New or recurrent splenomegaly
Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions
New 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
Bone marrow	New or recurrent involvement
Abbreviations: CT, computed tomography; IHC, immunohistochemistry; LDi, longest transvers diameter of a lesion; PPD, cross product of the LDi and perpendicular diameter; SDi. shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions	

Appendix 5 Strong CYP3A Inhibitors and Inducers

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

Abbreviation: 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.

Source: FDA Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

Appendix 6 Medications to be Used with Caution (Sensitive CYP2C8, CYP2C9, and CYP2C19 Substrates or CYP2C8, CYP2C9, and CYP2C19 Substrates With a Narrow Therapeutic Index)

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

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

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

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for drug interaction information or contact the medical monitor of the protocol.

Source: FDA Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012

Appendix 7 ECOG Performance Status

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

Appendix 8 New York Heart Association Classification

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

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

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