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)

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-205
Study 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)
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CCI [redacted]	[redacted]
B+R	bendamustine plus rituximab
BID	twice a day
BOR	best overall response
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
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 bone marrow recovery
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
IEC	Independent Ethics Committee
IGHV	immunoglobulin variable region heavy chain
IND	Investigational New Drug
IRB	Institutional Review Board

Abbreviation	Definition
IRC	Independent Review Committee
IRT	Interactive Response Technology
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nPR	nodular partial response
ORR	overall response rate
CCI [redacted]	[redacted]
PD	Progressive disease
PO	orally
PFS	progression-free survival
CCI [redacted]	[redacted]
PR	partial response
PR-L	partial response with lymphocytosis
PRO	patient-reported outcome
R/R	relapsed or refractory
SAE	serious adverse event
SD	stable disease
SE	Standard error
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
TEAEs	treatment emergent adverse events
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-3111-205. The focus of this SAP is for the planned analysis specified in the study protocol. The plan is written in accordance with protocol version 2.0 dated 25 October 2017.

CCI [redacted]

2 STUDY OVERVIEW

This is a single-arm, open-label, multicenter Phase 2 study in subjects with confirmed diagnosis of CLL/SLL who have relapsed or failed to achieve at least PR 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.

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 Independent Review Committee (IRC) review in accordance with Modified International Workshop on CLL (IWCLL) Guidelines (Hallek et al, 2008; Hallek et al, 2012; Hallek et al, 2013; 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.

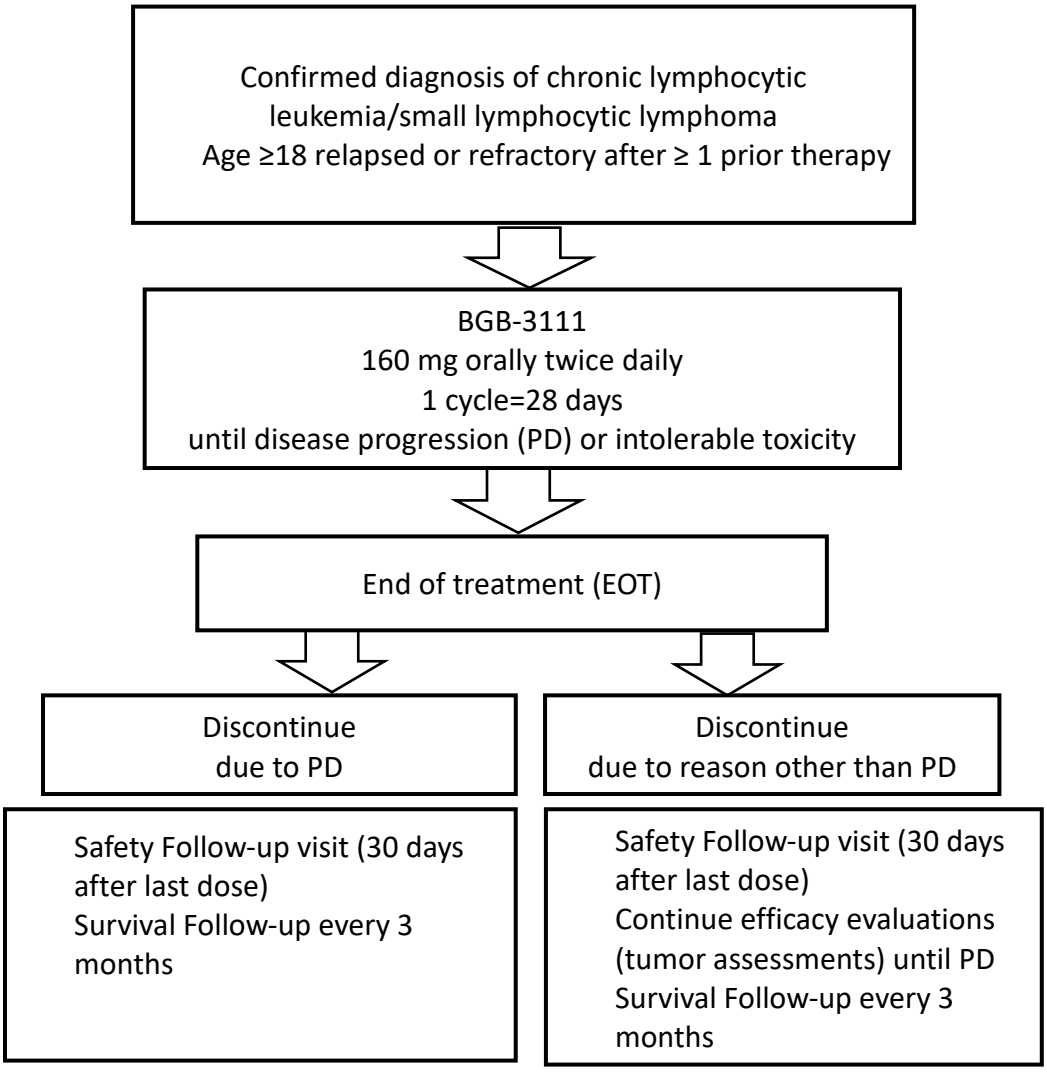
Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations. Screening evaluations can be repeated within the screening period.

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. 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



3 STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 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

3.3 CCI

[redacted]

4 STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint of the study is the rate of objective response, as determined by IRC, defined as the achievement of PR, including nPR, PR-L, CR, or CRi according to the modified 2008 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).

4.2 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 date 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 and dose reduction

4.3 CCI

[redacted]

CCI [redacted]

5 SAMPLE SIZE CONSIDERRATIONS

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%).

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

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

The Per-Protocol Population includes patients who received any dose of BGB-3111 and had no major protocol deviations. Criteria for exclusion from the Per-Protocol Population will be determined and documented before the database lock for the primary analysis.

CCI [redacted].

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day will be calculated in reference to the date of the first dose of study drug (Cycle 1 Day 1). For assessments conducted on or after Cycle 1 Day 1, study day will be calculated as assessment date –date of Cycle 1 Day 1 + 1. For assessments conducted before the date of Cycle 1 Day 1 of study drug, study day is calculated as assessment date – date of Cycle 1 Day 1 of study drug. There is no study day 0.

In the situation where the event date is partial or missing, Study Day and any corresponding durations will be presented based on the imputations specified in Appendix 1.

The treatment duration will be calculated as date of the last dose of study drug – date of Cycle 1 Day 1 of study drug + 1.

Baseline: Unless otherwise specified, a baseline value related to CLL/SLL disease assessment is defined as the last non-missing value collected within 28 days before Cycle 1 Day 1. Other baseline value, such as demographics, CLL/SLL treatment history, and pertinent medical history etc. is defined as last available value before Cycle 1 Day 1.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, first and third quartiles and range (minimum and maximum).

6.2.3 Handling of missing data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures as provided in Appendix 1.

When summarizing categorical variables, subjects with missing data are generally included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

If the start day of a subsequent anti-cancer therapy is missing, it will be assumed to be the first day of the month.

If only the day of death date is missing, the death will be assumed to be on the first day of the month if the last known alive data is earlier. If the last known alive date is later than the first day of the month, then the death date will be assumed to be the last known alive date plus 1 day.

No imputation of AE grades will be performed. TEAEs with missing CTCAE grade will only be summarized in the all-grades column.

If the assessment of the relationship of an AE to study treatments is missing, then the AE is assumed to be related to the study treatments in the safety analysis, but no imputation should be done at the data level.

6.2.4 Adjustments for Covariates

No adjustments for covariates are planned for primary and secondary analyses in the study. Baseline factors may be used in the model as covariates as supportive analyses for endpoints.

6.2.5 Multiple Comparisons/Multiplicity

Not applicable.

6.2.6 Data Integrity

Before pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

Assessment for progression and disease response is performed centrally by the IRC. The IRC data flow and workflow are described in the IRC charter.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Subject Disposition

The number (percentage) of subjects screened, treated, discontinued from study drugs and discontinued from the study will be summarized. The primary reason for end of treatment (study drug discontinuation) and end of study will be summarized by categories.

6.3.2 Protocol Deviations

Important protocol deviation criteria will be established and subjects with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized for all enrolled patients. They will also be listed by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the safety population. Variables include age (continuous and <65 vs. ≥65), gender, height, weight, cancer type, time since diagnosis, prior line(s) of therapy for CLL/SLL, Eastern Cooperative Oncology Group (ECOG) performance status, Binet stage, baseline Rai stage, IGHV mutational status, presence or absence of disease-related constitutional symptoms, lymphadenopathy, hepatomegaly, splenomegaly, Bulky disease (LDi<5 cm vs. ≥5 cm and <10 cm vs. ≥10 cm), cytopenias (yes vs. no), β2-microglobulin (≤3 mg/L vs >3 mg/L), blood lymphocytes, % of lymphocyte and tumor cell involvement in bone marrow biopsy for CLL and SLL patients respectively, platelet count, hemoglobin, neutrophils, serum immunoglobulins, coagulation, del(17p), del(13q), del(11q), trisomy 12, CCI , and other selected hematology and chemistry lab measures.

6.3.4 Prior Anti-Cancer Drug Therapies and Surgeries

The lines of prior anti-CLL/SLL drug therapies, prior anti-CLL/SLL radiotherapy and prior anti-CLL/SLL surgeries will be summarized. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

6.3.5 Prior and Concomitant Medication and Therapy

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes, and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term by phase in the safety population. Prior medications are defined as medications that started before the first dose date. 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 or initiation of a new anti-cancer therapy.

6.3.6 Medical History

Medical History will be coded using MedDRA (version 20.0). The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety population.

6.4 EFFICACY ANALYSIS

Analysis of efficacy endpoints will be conducted in the safety population, unless otherwise specified.

6.4.1 Primary Efficacy Analyses

The primary efficacy endpoint is overall response rate (ORR) according to the 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 response and disease progression will be centrally reviewed by IRC, which will be the primary source for the ORR analysis. Criteria for PD and response categories, as well as the process and convention of the IRC, will be prospectively detailed in the IRC charter.

ORR is defined as the crude proportion of patients who achieve 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 (Furman et al 2014; Sorensen et al 1997). A binomial exact test will be performed to test the null hypothesis H_0: ORR=0.32 in the safety population using the significance level of 0.025 (1-sided). 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.

Associated 2-sided 95% Clopper-Pearson CI of ORR will be calculated to assess the precision of the rate estimate.

Best overall response is defined as the best response recorded from the date of Cycle 1 Day 1 of BGB-3111 until data cut or start of new anti-cancer treatment. Patients with no post-baseline response assessment (due to any reason) will be considered as non-responders. The proportion and its corresponding Clopper-Pearson 95% CI for complete response rate will also be presented.

The ORR analysis will be conducted no later than 12 months after the first dose of the last dosed patient. Sensitivity analyses will be performed for ORR in the patients achieve a BOR of PR or higher (i.e. excluding CLL patients with BOR of PR-L). ORR analysis based on investigator assessments will also be performed.

6.4.2 Secondary Efficacy Analyses

6.4.2.1 Progression-Free Survival

PFS is defined as the time from Cycle 1 Day 1 of BGB-3111 to the earlier of disease progression or death due to any cause:

PFS = (Disease Progression/Death Date – first dose Date +1) / 30.4375

For purposes of calculating PFS, the start date for progressive disease is the date at which progression was first observed.

The duration of PFS will be right-censored for patients who met 1 of the following conditions: 1) no baseline disease assessments; 2) starting a new anti-cancer therapy before documentation of disease progression or death; 3) death or disease progression immediately after more than 1 consecutively missed disease assessment visit; and 4) alive without documentation of disease progression before the data cutoff date. For such patients, the primary analysis of PFS will be right-censored according to the convention described in Table 1. These conventions are based on 2012 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》.

PFS will be based on the IRC assessments. PFS as assessed by investigator will also be analyzed as sensitivity analyses.

Table 1: Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anti-cancer treatment started before documentation of PD or death	Date of last disease assessment prior to or on date of new anti-cancer treatment	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

The distribution of PFS, including median PFS and PFS rate at selected timepoints such as 3 and 6 months, will be summarized descriptively using the Kaplan-Meier method. The 95% confidence interval for median and other quartiles of PFS will be generated by using Brookmeyer method (Brookmeyer and Crowley 1982), whereas the 95% confidence interval for PFS rate at selected timepoints will be generated by using Greenwood formula (Greenwood 1926). Duration of follow-up for PFS will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).

6.4.2.2 Duration of response

The duration of overall response will be calculated for patients who achieve CR, CRi, nPR, PR, or PR-L. For such patients, the duration of overall response is defined as the number of days from the earliest date of the start of CR, CRi, nPR, PR, or PR-L, until the first date that progressive disease is objectively documented or death due to any cause.

DOR will be right censored for patients who achieve CR, CRi, nPR, PR, and PR-L based on the censoring conventions defined previously for the PFS analysis. The distribution of DOR will be summarized descriptively using the same methods used for PFS analysis. Median follow-up for DOR will be estimated according to the Kaplan-Meier estimate of potential follow-up also termed "reverse Kaplan-Meier" (Schemper and Smith 1996).

DOR will be based on the IRC assessments. DOR as assessed by investigator will also be analyzed as sensitivity analyses.

6.4.2.3 Time to Response

Time to response for responders (CR, CRi, nPR, PR, or PR-L) is defined as the time interval between Cycle 1 Day 1 and the date of the earliest qualifying response. TTR will be summarized by sample statistics such as mean, median and standard deviation for responders only. TTR will be based on the IRC assessments. TTR as assessed by investigators and based on patients with a BOR of PR or higher for CLL will also be analyzed as sensitivity analyses.

6.4.3 Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups, as appropriate. Within group values (rates for ORR/medians for PFS) will be presented in forest plots. The example of baseline variables for the subgroup analysis are below:

- Age (< 65 years vs ≥ 65 years)
- Gender (male vs female)
- Histology diagnosis (CLL vs SLL)
- Binet stage (C vs A or B)-
- Rai stage (Stage 0-II vs III-IV)
- ECOG-PS (0 vs ≥1)
- Prior line of therapy for CLL/SLL (1 vs ≥2)
- Refractory to last systemic therapy (Yes vs No)

- Bulky disease (LDi < 5 cm vs ≥ 5 cm and LDi < 10 cm vs ≥ 10 cm)
- IGHV mutational status (mutated vs unmutated)
- Elevated LDH at baseline (No (≤ ULN) vs Yes (> ULN))
- Cytopenias at baseline (Yes vs No)
- Chromosome 17p deletion (Yes vs No)
- Chromosome 13q deletion (Yes vs No)
- Chromosome 11q deletion (Yes vs No)
- Trisomy 12 (Yes vs No)
- CCI [redacted]
- Serum β2 – microglobulin (≤ 3 mg/L vs > 3 mg/L)

The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

6.4.4 CCI [redacted]

[redacted]

6.5 Safety Analyses

All safety analyses will be performed in the safety population. The study will set up a Safety Monitoring Committee (SMC). The SMC will monitor safety data according to the SMC charter (Appendix 5) periodically throughout the study.

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. The incidence of treatment-emergent adverse events (TEAEs), laboratory values (CBC, serum chemistry, and coagulation), vital signs, physical exams and ECG findings will be summarized using descriptive

statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables).

6.5.1 Extent of Exposure

Extent of exposure to BGB-3111 will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (date of last study drug administration-date of first study drug administration+1) (days), cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity (%).

For each patient, the relative dose intensity (actual vs planned) of BGB-3111 will be calculated. The average relative dose intensity for BGB-3111 will be calculated by summarizing the relative dose intensity for individual patients. These results will be provided to determine the presence of any major differences for the planned vs actual dose and schedule.

The number (and percentage) of patients with dose reduction, dose interruption, and drug discontinuation will be summarized with the respective reasons. The cycles in which dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of dose modifications will be summarized by categories.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA Version 20.0 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 starts or increases in severity on or after the date of the first dose of study drug is administered and within 30 days of the last administration of study drug or the start of new anti-cancer therapy, whichever occurs earlier. Missing and partially missing AE start dates will be imputed according to the specifications described in Appendix 1. 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.

TEAEs will be summarized based on the number and percentage of patients experiencing events by MedDRA system organ class and preferred term. The causal relationship between the occurrence of an AE and each treatment will be judged by the investigator. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and/or strongest causal relationship to each treatment will be used for purposes of incidence tabulations.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. AEs of special interest (AESI) include hemorrhage, major hemorrhage defined as any serious or grade ≥ 3 bleeding of any site, or central nervous system (CNS) bleeding of any grade,

atrial fibrillation, hypertension, second primary malignancies, diarrhea, tumor lysis syndrome, infection, opportunistic infection, neutropenia, thrombocytopenia, and anemia. The AESI categories are subject to change if warranted to better represent BGB-3111 safety.

Tabular summaries of the following AE will also be provided:

- TEAEs
  - by system organ class
  - by preferred term in decreasing frequency
  - by AEs of special interest
- SAEs
  - by system organ class
  - by AEs of special interest
- Treatment-related TEAEs
- TEAEs with grade 3 or above
- TEAEs with fatal outcome
- Treatment-related SAEs
- TEAEs resulting in discontinuation, reduction, or interruption of BGB-3111

Patient data listings of all AEs will be provided.

6.5.2.1 Exposure-Adjusted Incidence Rates (EAIR)

An exposure adjusted analysis is also planned to analyze AESIs. The analysis restricts on the occurrence of the first event per patient and ignores the existence of later (multiple) events as these cannot be assumed to occur independent of previous events.

The incidence rate for a patient is derived from the duration of treatment exposure of that patient. A patient's duration of exposure is given either 1) by the time when the event has occurred (non-censored data), or 2) by the total duration of treatment in case the patient does not show the adverse event of interest (censored data). Depending on whether a patient has an adverse event or not, the duration of exposure enters the denominator in its non-censored or censored form, respectively.

The average EAIR per AESI considers the first event per patient per AESI only, and the corresponding exposure time in the denominator:

$$EAIR_{AESI} = \frac{\sum_{i=1}^{n} TEAE_{AESI,i}}{\sum_{i=1}^{n} t_{AESI,i}}$$

Whereby $TEAE_{AESI,i}$ represents the first TEAE among all AESI TEAEs of patient i and t_i as time when the TEAE occurs (non-censored data) or total duration of treatment if no event occurs (censored data).

6.5.3 Laboratory Values

CBC and serum chemistry values will be evaluated for each laboratory parameter. 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. 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 NCI-CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. 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. Number (percentage) of patients with abnormal postbaseline laboratory values will be summarized.

The incidence of grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by cycle and across all treatment cycles.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], pulse rate, temperature, and weight) and changes from baseline will be presented by visit for all visits. Blood pressure will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades.

6.5.5 Electrocardiograms (ECG)

ECG assessments will be performed at the screening visit, pre-dose (within 30 min of dose) and C[redacted]

Descriptive statistics for ECG parameters will be presented. Overall interpretation of ECG will be summarized.

6.5.6 ECOG

ECOG scores will be summarized by visit.

6.6 CCI [redacted]

[redacted]

6.7 CCI

CCI [redacted]

7 INTERIM ANALYSES

Not applicable.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9 REFERENCES

CCI [redacted]

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10 APPENDIX

10.1 APPENDIX 1 IMPUTATION OF MISSING/PARTIALLY MISSING DATES

Missing data will not be imputed unless otherwise specified. The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:
If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first day of the month
- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If end date is completely missing, do not impute

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

10.2 APPENDIX 2 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.

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.

10.3 APPENDIX 3 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	

10.4 APPENDIX 4 SAFETY MONITORING COMMITTEE CHARTER

10.5 APPENDIX 5 INDEPENDENT REVIEW COMMITTEE CHARTER