STATISTICAL ANALYSIS PLAN

Study Protocol Number:	**BGB-3111_GA101_Study_001**
Study Protocol Title:	**A Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignancies**
Date:	03Aug2020
Version:	1.0

SIGNATURE PAGE

Author:

[redacted]

Signat
Date:

[redacted]

Approval:

[redacted]

Signature
Date: 0

[redacted]

Signature
Date: 11

[redacted]

Signature
Date: 15

[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	Adverse events
AUC	Area under the plasma concentration-time curve
BID	Bis in die (twice a day)
BMI	Body mass index
BTK	Bruton tyrosine kinase
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
CR	Complete response
CT	Computed tomography
DBP	Diastolic blood pressure
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FDA	Food and Drug Administration
FL	Follicular lymphoma
GCB	Germinal center B-cell-like
GRK	G-protein coupled receptor kinase
HCV	Hepatitis C virus

HER	Human epidermal growth factor receptor
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRR	Major response rate
MTD	Maximal tolerated dose
MZL	Marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PFS	Progression-free survival
PR-L	Partial response with lymphocytosis
QD	Quaque die (once a day)
RP2D	Recommended phase 2 dose
RT	Richter's transformation
SAEs	Serious adverse events
SBP	Systolic blood pressure
SLL	Small lymphocytic lymphoma
SMC	Safety Monitoring Committee

$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum observed plasma concentration
Vd/F	Apparent volume of distribution
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia

1 INTRODUCTION

This statistical analysis plan (SAP) describes the detailed plan for the analysis of data used for the evaluation of safety and efficacy for the zanubrutinib GA101 Study 001. This document is based on version 6 of the protocol, dated 03 January 2019.

2 STUDY OVERVIEW

This is a two-part, phase 1b, multi-center open-label study designed to determine the safety, tolerability, and clinical activity of zanubrutinib in combination with obinutuzumab. The study is conducted in two sequential parts. Part 1 evaluates the safety of two dose regimens of zanubrutinib in combination with obinutuzumab. Part 2 evaluates the antitumor activity of the recommended phase 2 dose (RP2D) of zanubrutinib in combination with obinutuzumab in subjects with treatment-naïve (TN) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), relapsed/refractory (R/R) CLL/SLL, R/R non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL), R/R follicular lymphoma (FL), R/R mantle cell lymphoma (MCL), R/R Waldenström macroglobulinemia (WM), or R/R marginal zone lymphoma (MZL).

The study consists of a screening period, treatment, a 28-day safety follow-up, and follow-up for disease status and survival. Subjects who discontinue study drug due to reasons other than disease progression are to remain in the study and be followed every 3 months until the subject exhibits first progression, withdraws consent, death or study closure, whichever occurs first. Once a subject progresses or starts alternative anti-cancer therapy, he/she will be contacted every 3 months, by telephone, to assess survival until death, withdrawal of consent or study closure, whichever occurs first.

Part 1: Safety Evaluation

This part of the study evaluated two dose regimens of orally administered zanubrutinib (320 mg QD and 160 mg BID [added per Amendment Version 3.0]) in combination with intravenously administered obinutuzumab (100 mg IV on Cycle 1 Day 2, 900 mg IV on Cycle 1 Day 3, 1000 mg IV on Cycle 1 Days 9 and 16, and 1000 mg IV on Day 1 of cycles 2-6) in cohorts of 6 subjects each. If there were 2 or more dose-limiting toxicities (DLTs) in a 6-subject cohort in either regimen, the dose level was considered to have exceeded the maximum tolerated dose (MTD) and a reduced dose level of zanubrutinib (160 mg QD or 80 mg BID) was to be evaluated in combination with obinutuzumab in another cohort of 6 subjects. Further reductions of zanubrutinib dose level were allowed until a safe dose combination was identified. The period for DLT assessment was 29 days from first administration of zanubrutinib. In the event that a

MTD was not exceeded, both 320 mg QD and 160 mg BID were to be evaluated for Part 2 of the study.

Zanubrutinib was administered orally with or without food every day in each cycle (29 days for Cycle 1 and 28 days for Cycles 2 and each cycle thereafter) until disease progression, death, unacceptable toxicity, other reasons for treatment discontinuation, or study closure, whichever occured first.

The continuous safety evaluation was performed by a Safety Monitoring Committee (SMC) composed of the Sponsor, the Sponsor's medical monitor, the coordinating investigator, and the contract research organization (CRO) medical monitor. The SMC composition and responsibilities are detailed in the SMC charter. The SMC was responsible for the determination of regimens to be administered during the study.

At the time of approval of this document, enrollment and dose evaluation of Part 1 has been completed. A cohort of 6 subjects were assigned to both regimens and no DLT was identified in either cohort.

Part 2: Indication Specific Expansion

In Part 2, the 2 zanubrutinib regimens (320 mg QD and 160 mg BID) were investigated in 5 expansion cohorts (revised per Amendment Version 4.0) with histology type of tumor defined as below. Based on the safety, tolerability, PK, and antitumor activity data from the safety evaluation part (Part 1) of the study:

- Cohort 1: TN CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 2: R/R CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 3: R/R non-GCB DLBCL, defined by Hans algorithm (approximately 20 subjects divided by the 2 regimens)
- Cohort 4: R/R FL, MCL, MZL, and WM (approximately of 20 subjects divided by the 2 regimens)
- Cohort 5: R/R FL (approximately 40 subjects in 160 mg BID. About 10-15 of them were to meet double-refractory criterion, defined as refractoriness to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractoriness was defined per protocol as less than a partial response or progression of disease within 6 months after completion of a prior therapy, added per Amendment Version 4.0).

After the SMC confirmed that the 6 subjects in 160 mg BID regimen passed Part 1 DLT test, all new eligible subjects were enrolled into 160 mg BID regimen in each of the 5 cohorts until the

total number of that cohort reached the pre-specified number. Subjects enrolled in zanubrutinib 320 mg QD dose regimen had the option to switch to 160 mg BID.

Zanubrutinib was administered orally with or without food every day in each cycle (28 days for each cycle) until disease progression, death, unacceptable toxicity, other reasons for treatment discontinuation, or study closure, whichever occurs first.

Obinutuzumab was administered intravenously for up to 6 cycles consistent with the

U.S. label regimen:

- Day 2 Cycle 1: 100 mg obinutuzumab
- Day 3 Cycle 1: 900 mg obinutuzumab
- Day 9 and Day 16 Cycle 1: 1000 mg obinutuzumab
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab

The safety evaluation by the SMC was to be performed on as needed basis (see the SMC Charter) but at a minimum of every 6 months to review all subjects enrolled, or when there was any significant safety finding. Any treatment-related death would also trigger review by the SMC. The SMC would determine whether it is safe to proceed with the study. Approximately 120 subjects were to be enrolled and treated during Part 2.

At the time of approval of this document, enrollment of subjects in the 5 expansion cohorts of Part 2 was complete and a total of 107 subjects were enrolled into one of the 5 cohorts.

3 STUDY OBJECTIVES

3.1 PART 1

Primary Objectives

- To evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab.
- To determine the MTD and/or the RP2D of zanubrutinib, in combination with obinutuzumab, when given continuously orally.

Secondary Objectives

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.
- To characterize the pharmacokinetics (PK) of zanubrutinib and obinutuzumab when administered in combination.

Exploratory Objectives

[redacted]

3.2 PART 2

Primary Objectives

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.

Secondary Objectives

- To further evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab.
- To further characterize the PK of zanubrutinib and obinutuzumab when administered in combination.

Exploratory Objectives

[redacted]

4 STUDY ENDPOINTS

4.1 PART 1

Primary Endpoints

- Incidence, nature, and severity of adverse events (AEs), serious adverse events (SAEs) per the NCI-CTCAE Version 4.03, clinical laboratory abnormalities, deaths and cause of death, and DLTs.
- Incidence of DLTs in Part 1 of the study according to the MTD/RP2D evaluation process.

Secondary Endpoints

- For zanubrutinib, area under the plasma concentration-time curve from zero to the last

measurable concentration (AUC_{last}), area under the plasma concentration-time curve from zero to infinity (AUC), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F) on Cycle 1 Day 1 and Cycle 2 Day 1.

- For zanubrutinib, after steady-state: $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.
- For obinutuzumab, plasma concentration prior to start of the infusion, and at 4 hours (end of infusion) on Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 9, Cycle 1 Day 16, as well as Day 1 Cycles 2, 4, and 6.

Exploratory Endpoints

[redacted]

4.2 POOLED PART 1 AND PART 2

Primary Endpoint

- Frequency and durability of objective responses for each of the specified disease cohorts as per the standard International Working Group (IWG) Criteria for each diagnose in terms of BOR.

Secondary Endpoints

Efficacy Secondary Endpoints

- Frequency and durability of objective responses for each of the specified disease cohorts as per the standard International Working Group (IWG) Criteria for each diagnose in terms of PFS, DOR, TTR, and OS.

Safety Secondary Endpoints

- AEs, SAEs per the NCI-CTCAE version 4.03 (or higher), physical examination, and laboratory measurements.
- Pharmacokinetic parameters for zanubrutinib and obinutuzumab as described for Part 1,

including AUC_{last}, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, V_d/F, $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.

Exploratory Endpoints

[redacted]

In addition to the endpoints defined above, the following efficacy endpoints are defined for pooled Part 1 and Part 2 subjects for each disease type.

WM

Response criteria for subjects with WM are based on modified Response Assessment in WM: Update from the VIth International Workshop (Owen, 2013).

Primary Efficacy Endpoint

- Rate of VGPR or better

Secondary Efficacy Endpoints

- Rate of major response (PR or better)
- Rate of overall response (MR or better)
- Duration of VGPR or better, duration of major response, and duration of overall response
- Time to VGPR or better, time to major response, and time to overall response

CLL/SLL

Response criteria for subjects with CLL/SLL are based on Guidelines for the Diagnosis and Treatment of CLL (Halleck, 2008) and Novel Targeted Agents and the Need to Refine Clinical Endpoints in CLL (Cheson, 2012) for CLL and Modified Lugano Classification for NHL (Cheson, 2014) for SLL.

Primary Efficacy Endpoint

- Rate of overall response (PR-L or better)

Secondary Efficacy Endpoint

- Rate of CR

- Rate of PR or better
- Duration of CR, duration of PR or better, duration of overall response
- Time to CR, time to PR or better, time to overall response
- Number and percentage of CLL subjects with anemia (hemoglobin $\leq 110\ g/L$), neutropenia (neutrophil count $\leq 1.5 \times 10^9/L$), or thrombocytopenia (platelet count $\leq 100 \times 10^9/L$) at baseline and among these subjects who achieved hematologic normalization after treatment , respectively.

Exploratory Efficacy Endpoint

[redacted]

FL and Other B-cell Lymphoid Malignancies (MCL, MZL, non-GCB DLBCL)

Response criteria for subjects with MCL are based on Modified Lugano Classification for NHL (Cheson, 2014). Response criteria for other B-cell lymphoid malignancies are based on the modified Lugano classification for NHL (Cheson, 2014).

Primary Efficacy Endpoint

- Rate of overall response (PR or better)

Secondary Efficacy Endpoint

- Rate of CR
- Duration of CR and duration of overall response
- Time to CR and time to overall response

5 SAMPLE SIZE CONSIDERATIONS

Part 1

The number of dose regimens and the emerging zanubrutinib and obinutuzumab toxicities will determine the sample size. It is anticipated that approximately 12 subjects are required to establish the selected treatment regimen of zanubrutinib when administered in combination with obinutuzumab in Part 1.

Part 2

Approximately 120 subjects will be enrolled in the five disease cohorts in Part 2. The number of subjects in each cohort is described in Section 2. Enrollment in certain arms may be closed prematurely due to safety intolerability to zanubrutinib at the discretion of Sponsor or SMC.

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

Safety Analysis Set

The safety analysis set will include all subjects who receive at least 1 dose of zanubrutinib and/or obinutuzumab. The safety analysis set will be the primary analysis set for the efficacy and safety analyses unless otherwise noted.

DLT Evaluable Set

The DLT Evaluable set will include all subjects who experienced a DLT during Cycle 1, or subjects who received at least 80% of the planned doses (80%*29*320 mg) of zanubrutinib and missed no more than one administration (one full dose) of obinutuzumab during Cycle 1 (interruption of obinutuzumab infusion does not count as long as the full dose was administered). DLT summary will be performed for Part 1 only.

PK Analysis Set

The PK analysis set will include all subjects who have received at least the first administration of zanubrutinib and provided PK samples as per protocol (without any significant protocol deviation affecting the PK blood sample)[1] following the first treatment of zanubrutinib on Cycle 1 Day 1.

PD Analysis Set

The PD analysis set will include all subjects who have received at least the first administration of zanubrutinib and provided PD samples as per protocol following the first treatment of zanubrutinib on Cycle 1 Day 1.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

Limited safety and efficacy analysis will be performed by Part 1 and Part 2 separately.

[1] Listings of significant protocol deviations affecting the PK blood sample will be provided separately.

For Part 1, limited safety analyses will be summarized by the following dose level/schedule of zanubrutinib administration:

- 160 mg BID
- 320 mg QD
- Part 1 overall.

For Part 2, limited safety and efficacy analysis by disease type may be performed similarly to the pooled part 1 and part 2 set as described below.

Complete safety and efficacy analyses will be performed for the pooled Part 1 and Part 2 set.

Efficacy and safety will be summarized by the following disease type and status:

- CLL/SLL
  - R/R
  - TN
  - Overall
- WM
- MCL
- FL
- MZL
- DLBCL (including all non-GCB DLBCL and one GCB DLBCL) [2]
- Overall.

Moreover, for the pooled Part 1 and Part 2 set, safety will be summarized by the following dose level/schedule of zanubrutinib administration as well:

- 160 mg BID
- 320 mg QD

[2] While the disease type GCB DLBCL was not allowed by the protocol, one subject with this diagnosis was enrolled, treated, and followed for efficacy and safety. This subject will be combined with non-GCB DLBCL subjects in the efficacy and safety analyses and specified in a footnote.

- Part 1 and Part 2 overall.

A subject will be included in the dose level/schedule group per the first dose received unless otherwise specified.

Descriptive statistics include n, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables and n (%) for categorical variables.

DLT (if any) will be summarized by dose schedule.

All calculations and analyses will be conducted using SAS® (SAS Institute Inc., Cary, NC, USA) version 9.3 or above.

6.2.1 Definitions and Computations

Study treatment for this study is zanubrutinib and/or obinutuzumab.

Study day is calculated relative to the date of the first administration of either study treatment. For assessments conducted on or after the date of the first administration of study treatment, study day will be calculated as assessment date – date of first administration + 1. For assessments conducted before the date of the first administration of study treatment, study day is calculated as assessment date – date of first administration. There is no study day 0.

Treatment duration is calculated as (date of end of treatment – date of first administration of study treatment + 1).

Baseline is defined as the last non-missing value collected on or before the first administration of study drug unless otherwise specified.

Study follow-up time is defined as the time from first dose date to the death date or end of study date for patients discontinued from study (whichever occurs first), or the database cutoff date for ongoing patients.

Definitions of efficacy variables are provided in Section 6.4 and definitions of safety variables are provided in Section 6.5.

6.2.2 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. Specific rules for handling of missing or partially missing dates for diagnosis, progression/relapse to prior therapy, adverse events, and prior/concomitant medications/procedures are provided in the Appendix A: Missing Data Imputation Rule.

When summarizing categorical variables, patients 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, patients with missing data are not included in calculations unless otherwise specified.

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 treatment in the safety analysis summary. No imputation will be done in the AE listings.

6.2.3 Adjustment for Covariates

With possible exception of exploratory analyses, no adjustments for covariates are planned for this study. Baseline factors may be included in the models used for these exploratory analyses.

6.2.4 Multiplicity Adjustment

No formal hypothesis testing is planned for this study. Adjustment for multiplicity is not planned.

6.2.5 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 essential data should be complete and reviewed up to a pre-specified cutoff date. Critical consistency checks and appropriate source data verification should be completed according to the final data extraction plan.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Subject Disposition

The following subject disposition information will be summarized:

- Number of treated subjects who received any amount of zanubrutinib or obinutuzumab.
- Number (%) of treated subjects who remained on treatment
- Number (%) of treated subjects who discontinued treatment
    - Reasons for treatment discontinuation

- Number (%) of treated subjects who discontinued study
    - Reasons for study discontinuation
- Number (%) of treated subjects who remained on study

The number (%) of treated subjects by country and site, and the study follow-up time will also be summarized.

6.3.2 Protocol Deviations

Criteria for important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized by deviation category. A listing of important protocol deviations will also be provided.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including the following will be summarized using descriptive statistics:

- Age (years) and age group (<65 vs. ≥65 and <75 vs. ≥75)
- Gender
- Race and ethnicity
- Height (cm), weight (kg), and body mass index (BMI, kg/m^2)
- Vital signs (blood pressure, pulse, and temperature)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2)

6.3.4 Disease History

The disease characteristics at baseline including the following will be summarized if data permits:

- Prior treatment status (treatment naïve, relapsed/refractory)
- Time (months) since the initial diagnosis to first dose
- Bulky disease
- Disease-related B symptoms
- Bidimensional measurement of nodal, liver, and spleen
- Tumor or lymphoid cell infiltration

- Serum immunoglobulin (IgM, IgA, IgG, Serum EPG, Monoclonal IgM by IFE)
- IgM category (< 40 g/L, ≥ 40 g/L)
- Hemoglobin and category (≤ 110 g/L, > 110 g/L)
- Platelet count and category (≤100 $x10^9$/L, > 100 $x10^9$/L)
- Absolute neutrophil count and category (≤1.5 $x10^9$/L, > 1.5 $x10^9$/L)
- Absolute lymphocytes count
- For CLL:
    - RAI and Binet clinical stage
    - IgHV mutational status (mutated/unmutated)
    - P53 mutational status (negative, positive [wild type, mutant, unknown, other])
    - Positive chromosomal abnormalities (17p, 11q, 13q, +12, complex karyotype [defined as 3 or more unrelated chromosome abnormalities])
- For FL:
    - International Prognostic Index for Follicular Lymphoma risk factors and risk category
    - Rituximab-refractory status (refractory, not refractory or unknown)
    - Refractory status to the most recent line of therapy (refractory, not refractory or unknown)
    - Progression of disease within 24 months of starting the first line of therapy (yes, no or unknown)
    - Progression of disease within 6 months of starting any prior therapy (yes, no or unknown)
    - Progression of disease within 12 months of starting any prior therapy (yes, no or unknown)

Refractoriness (including rituximab-refractory) is defined as less than a partial response or progression of disease within 6 months after completion of the prior therapy.

- For DLBCL: International Prognostic Index risk factors and risk category

6.3.5 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0 or higher). The number (%) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class (SOC) and preferred term (PT).

6.3.6 Prior Anti-Cancer Therapies, Radiotherapies, or Surgeries

The following information related to prior therapy for lymphoma will be summarized by Anatomical Therapeutic Chemical (ATC) medication class Level 2 and World Health Organization Drug Dictionary (WHO DD) drug codes (version March 2017 or later) preferred name:

- Number of regimens of prior anti-cancer therapies
- Time (months) from the end of the last line of prior anti-cancer therapy to first dose of study drug
- Best response to the last line of prior anti-cancer therapy
- Prior anti-cancer radiotherapy
- Prior anti-cancer surgeries

6.3.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes version March 2017 or later and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

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 treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after the patient's last dose or initiation of a new anti-cancer therapy. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Appendix A: Missing Data Imputation Rule will be used.

The number (%) of subjects reporting prior medications and concomitant medications will be summarized by ATC medication class Level 2 and WHO DD preferred name.

6.4 Efficacy Analysis

The primary summaries of the efficacy data will be performed in the safety analysis set. The response and progression status will be determined by the investigator using the appropriate

disease-specific criteria defined in the protocol. The efficacy endpoints for pooled Part 1 and Part 2 by disease type are listed in Section **Error! Reference source not found.**.

6.4.1 Best Overall Response and Response Rates

A subject's best overall response (BOR) is the best response recorded throughout the study (prior to data cutoff). Subjects without post-baseline disease assessment will be considered as non-responders. Response rate is a crude proportion of patients with best overall responses in the corresponding response categories. Responses after the initiation of any new anti-cancer therapy, rollover to LTE or the first occurrence of disease progression will not be considered for the analysis of response rate.

The best overall response (number [%]) will be summarized. Moreover, each response rate with corresponding two-sided 95% exact binomial confidence interval (Clopper-Pearson method) will also be calculated.

6.4.2 Progression-free Survival

Progression-free survival (PFS) is defined as time (in months) from the start of study treatment to the first documented disease progression or death (due to any cause), whichever occurs first.

PFS will be right-censored for subjects who met one of the following conditions: 1) alive and no post-baseline disease assessment; 2) disease progression or death after one year since last disease assessment; 3) rollover to LTE and 4) alive without disease progression. For such subjects, the primary analysis of PFS will be right-censored according to the convention described in Table 1. The censoring rule is based on FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics' (2018, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics).

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

Situation	Date of Progression Event	Outcome
Alive and no post-baseline disease assessment	Date of the first dose of study drug	Censored
Alive and no PD before study discontinuation or rollover to LTE	Date of last disease assessment before study discontinuation or rollover to LTE	Censored
Death or PD after one year since last disease assessment	Date of last disease assessment	Censored

Death or PD between 2 planned disease assessments	Date of death or PD, whichever occurs first	Event
Death and no post-baseline disease assessment	Date of death	Event

Date of last disease assessment is defined as below:

- For CLL/SLL: date of the last response assessment[3], radiographic scan, targeted physical exam (liver, spleen, or lymph node), B symptoms assessment, or local hematology lab assessment (hemoglobin, platelet, neutrophil, or lymphocyte), whichever is the latest.
- For WM: date of the last response assessment[3] or IgM level test, whichever is later.
- For all other disease types (FL, MCL, MZL, and non-GCB DLBCL): date of the last response assessment[3], radiographic scan, or targeted physical exam (liver, spleen, or lymph node), whichever is the latest.

The distribution of PFS, including median and other quartiles and PFS rate at selected timepoints such as 12, 24, 36, 48 months, will be estimated using the Kaplan-Meier method. The 95% confidence interval for median and other quartiles of PFS will be generated by using Brookmeyer method, whereas the 95% confidence interval for PFS event free rate at landmark times will be generated by using the Greenwood formula. Duration of follow-up for PFS will be estimated by the reverse Kaplan-Meier method. Kaplan-Meier curves for PFS will also be generated.

6.4.3 Duration of Response

Duration of response (DOR) for responders (those whose best response was CR, VGPR, PR, or PR-L depending on the disease type, or other targeted responses) is defined as the time (in months) from the date of the earliest qualifying response to the date of PD or death due to any cause (whichever occurs earlier). The dates of progression and censoring will be determined as described in Section 6.4.2. DOR will be analyzed using the same methods as in the analysis of PFS. Responses after the initiation of new anti-cancer therapy, rollover to LTE or the first occurrence of disease progression will not be considered for the analysis of DOR.

[3] Prior to the protocol amendment 6, response assessment frequency after week 48 was at the discretion of the treating investigator when there was no sign of disease progression.

6.4.4 Time to Response

Time to response (TTR) for responders is defined as time (in months) from the start of the study treatment to the date of the earliest qualifying response. TTR will be summarized by descriptive statistics. Responses after the initiation of new anti-cancer therapy, rollover to LTE or the first occurrence of disease progression will not be considered for the analysis of TTR.

6.4.5 Overall Survival

Overall survival (OS) is defined as the time (in months) from the date of the start of the study treatment to death due to any cause. Subjects who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than death) will be censored at subject's last known alive date on or prior to data cutoff. OS will be analyzed using the same methods as in the analysis of PFS.

6.4.6 Subgroup Analyses

The primary and selected secondary endpoints for each disease type may be summarized in selected subgroups described in Section 6.3.3 and 6.3.4 as appropriate (i.e. when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined).

6.4.7 Other Endpoints

The following analyses may be performed if found to be necessary and data permits.

6.4.7.1 Hematologic Improvement for CLL

Number and percentage of CLL subjects with anemia (hemoglobin $\leq 110\ g/L$), neutropenia (absolute neutrophil count $\leq 1.5 \times 10^9/L$), or thrombocytopenia (platelet count $\leq 100 \times 10^9/L$) at baseline and among these subjects who achieved hematologic normalization after treatment will be estimated respectively along with corresponding 95% exact binomial CI.

Hematologic normalization refers to hemoglobin, absolute neutrophil count, or platelet count goes beyond $110\ g/L$, $1.5 \times 10^9/L$, $100 \times 10^9/L$, respectively.

6.4.7.2 Minimal Residual Disease Clearance Rate for CLL

The minimal residual disease (MRD) clearance rate, defined as the proportion of subjects who achieved negative MRD status after treatment, will be estimated with 95% exact binomial confidence interval for CLL/SLL subjects who achieved a CR and had MRD tested.

6.4.7.3 Correlation of Clinical Response with Prognostic and Biological Markers

The correlation of clinical response to zanubrutinib in combination with obinutuzumab with established prognostic (e.g., International Prognostic Index for DLBCL, adverse cytogenetics for

CLL) and biological markers (genomic alterations in non-GCB DLBCL) for the specific histology may be explored using logistic regression.

Other exploratory efficacy analyses will be based on review of the available efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) data. Further analyses to the PK, PD, and biomarkers data will be specified in a separate analysis plan.

6.5 SAFETY ANALYSES

All safety analyses will be provided for the safety analysis set. In addition to the study groups described in Section 6.2 summaries will be provided for the overall group combining all subjects in Part 1 and 2.

6.5.1 Extent of Exposure

The following measures of the extent of study drug exposure will be summarized:

- Starting dose and schedule of zanubrutinib
- Number (%) of subjects with dose reduced, drug interrupted (due to compliance issues, due to non-compliance issues[4]), and the corresponding reasons for zanubrutinib
- Number (%) of subjects with dose interrupted (full dose administered, full dose not administered) and the corresponding reasons for obinutuzumab
- Number of treatment cycles for zanubrutinib and obinutuzumab respectively
- Duration of study treatment in week for zanubrutinib, obinutuzumab, and a combination of zanubrutinib and obinutuzumab, respectively
- Cumulative dose of study treatment (mg) administered for zanubrutinib and obinutuzumab respectively
- Actual dose intensity (ADI, mg/day) and relative dose intensity (RDI, mg/day) of zanubrutinib
- ADI (mg/infusion) and RDI (mg/infusion) of obinutuzumab

Number of treatment cycles for zanubrutinib is defined as (duration of zanubrutinib treatment in days)/29 if duration of zanubrutinib treatment in days <= 29, and 1 + (duration of zanubrutinib treatment in days-29)/28 if duration of zanubrutinib treatment in days > 29. Duration of

[4] A list of key word search will be used to identify whether the interruption of zanubrutinib was due to compliance issues or not. The list of key words will be provided in the appendix.

zanubrutinib treatment in days is defined as the last zanubrutinib administration date – the first zanubrutinib administration date + 1.

Number of treatment cycles for obinutuzumab is defined as the number of cycles where patients received any amount of obinutuzumab.

Duration of zanubrutinib/obinutuzumab/combination in week is defined as (the last zanubrutinib/ obinutuzumab/ combination administration date – the first zanubrutinib/ obinutuzumab/ combination administration date + 1)/7.

The ADI of zanubrutinib is defined as the cumulative dose (mg) of zanubrutinib divided by the duration of zanubrutinib (day), which is defined as the last zanubrutinib administration date – the first zanubrutinib administration date + 1.

The RDI of zanubrutinib is defined as the ratio of ADI (mg/day) of zanubrutinib and the planned dose intensity (PDI, mg/day) of zanubrutinib, which is 320 mg/day.

The ADI of obinutuzumab is defined as the cumulative dose (mg) of obinutuzumab divided by the actual number of infusions of obinutuzumab.

The RDI of obinutuzumab is defined as the ratio of ADI (mg/infusion) of obinutuzumab and the PDI (mg/infusion) of obinutuzumab, which is (8000/9) mg/infusion.

6.5.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or increase in severity level on or after the first dose of study drug and within 30/90 days after the last dose of zanubrutinib/obinutuzumab or prior to the initiation of new anti-cancer therapy, whichever is sooner.

A treatment-related adverse event is an adverse event that is noted by the investigator as related to zanubrutinib or obinutuzumab.

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.

TEAE will be summarized based on the number (%) of subjects experiencing events by MedDRA SOC and PT. A subject reporting the same AE more than once will be counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT

combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to zanubrutinib for the event will be used in the incidence calculations.

An overall summary of the number and percentage of subjects will be presented for the following categories:

- With at least one TEAE
- With at least one grade 3 or higher TEAE
- With at least one treatment-related TEAE, defined as related to zanubrutinib or obinutuzumab by the investigator
- With at least one zanubrutinib-related TEAE
- With at least one obinutuzumab-related TEAE
- With at least one infusion-related TEAE
- With at least one treatment-related grade 3 or higher TEAE
- With at least one zanubrutinib-related grade 3 or higher TEAE
- With at least one obinutuzumab-related grade 3 or higher TEAE
- With at least one infusion-related grade 3 or higher TEAE
- With at least one fatal TEAE
- With at least one treatment-related fatal TEAE
- With at least one zanubrutinib -related fatal TEAE
- With at least one obinutuzumab-related fatal TEAE
- With at least one infusion-related fatal TEAE
- With at least one SAE
- With at least one treatment-related SAE
- With at least one zanubrutinib-related SAE
- With at least one obinutuzumab-related SAE
- With at least one infusion-related SAE
- With TEAE leading to dose reduction of zanubrutinib
- With TEAE leading to dose interruption of zanubrutinib

- With TEAE leading to dose interruption of obinutuzumab
- With TEAE leading to discontinuation of zanubrutinib
- With TEAE leading to discontinuation of obinutuzumab
- With at least one instance of DLT (no reported)

Summaries of all above TEAEs will also be provided by SOC and PT.

Moreover, summaries of all TEAEs, grade 3 or higher TEAEs, treatment-related TEAEs, and SAEs will also be provided by PT only and maximum severity.

An overall summary of the number and percentage of subjects will be presented for the following categories:

- With at least one AE of special interest (AESI)
- With at least one treatment-related AESI
- With at least one grade 3 or higher AESI
- With at least one treatment-related grade 3 or higher AESI
- With at least one serious AESI
- With at least one serious treatment-related AESI

Summaries of all above AESIs will also be provided by SOC and PT. Moreover, summaries of all AESIs will also be provided by PT only, and maximum severity.

Although Protocol V.6 stated that AESIs will be summarized by cycle, but this will not be done as it is not part of BeiGene normal procedures and standards.

An overall summary of death will be presented for the following categories:

- Total deaths
- Deaths within 30 days of last dose of study drug
- Deaths more than 30 days of last dose of study drug

Causes of death will also be summarized.

Listings of deaths, SAEs, TEAEs leading to zanubrutinib discontinuation and TEAEs leading to obinutuzumab discontinuation will be provided.

6.5.3 Laboratory Values

All hematology, serum chemistry, coagulation, and urinalysis results for each subject will be presented in data listings. The baseline value, post-baseline value and change from baseline for all hematology, serum chemistry, and coagulation parameters will be summarized at each scheduled visit.

Selected laboratory test results will be assigned toxicity grades using the IWCLL 2008 Grading Scale (Hallek et al 2008) for hematological toxicity in CLL/SLL patients and NCI CTCAE 4.03 for hematological toxicities in non-CLL/SLL patients and non-hematological toxicities of all patients. The laboratory parameters of interest for these summaries are (if available):

Hematology	**Serum Chemistry**		**Coagulation**
Hemoglobin (decrease)	Alanine transaminase (ALT) (increase)	Albumin (decrease)	Activated partial thromboplastin time (aPTT) (increase)
Platelets (decrease)	Aspartate transaminase (AST) (increase)	Uric Acid (increase)	International Normalized Ratio (INR) (increase)
WBC (increase, decrease)	Alkaline Phosphatase (increase)	Sodium (increase, decrease)	
Absolute Neutrophil Count (ANC, decrease)	Total Bilirubin (increase)	Phosphorus (decrease)	
Absolute Lymphocyte Count (increase, decrease)	Creatinine (increase)	Potassium (increase, decrease)	
	Calcium (increase, decrease)	Magnesium (increase, decrease)	
	Glucose (increase, decrease)		

For hypocalcemia and hypercalcemia, serum calcium will be corrected using the formula:

> Corrected calcium = Serum calcium + 0.8 * (4 – serum albumin) where serum calcium is recorded in mg/dL and serum albumin is recorded in g/dL.

Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded post-baseline will be presented. A summary of the number (%) of subjects with grade 3 or higher toxicity will be provided for each laboratory parameter of interest. A listing of all grade 3 or higher laboratory values will be provided. Box-whisker plots will be generated for parameters of interest.

Incidence of patients who met one or more of the Hy's law criteria will be summarized. A listing of patients that met one or more of the Hy's law criteria will be generated.

6.5.4 Physical Examination

Physical examination results will be listed without summary.

6.5.5 Echocardiogram

The overall evaluation and left ventricular ejection fraction (LVEF, %) at screening will be listed without summary.

6.5.6 Electrocardiograms (ECG)

The baseline value, post-baseline value and change from baseline for the PR, QRS, and QTc-B interval will be summarized at each scheduled visit. If triplicate readings are recorded at one visit the average of the readings for the visit will be used for the summary. It's expected that there may be a decrease in ECG testing implemented, based on the reduced ECG requirements in Protocol Amendment 6.

6.5.7 Vital Signs

The baseline value, post-baseline value and change from baseline for vital sign results including blood pressure, pulse, and temperature will be summarized at each scheduled visit. If triplicate readings are recorded at one visit the average of the readings for the visit will be used for the summary. Any clinically significant values will be reported by the investigator as AEs in the clinical study database.

6.5.8 ECOG

ECOG performance status will be summarized and listed at each visit. Shift tables assessing the ECOG performance status at baseline versus worst performance status post-baseline will be presented.

6.5.9 New Anti-Cancer Therapy

The number and percentage of subjects with at least one new anti-cancer therapy, and number of new anti-cancer treatments will be summarized. The initiation date of new anti-cancer therapy will be the earliest date of any new anti-cancer treatment, any new anti-cancer radiology, and any new anti-cancer surgery, taking from these 3 CRF forms: "Anti-cancer treatment on

(SURVIVAL) follow up", "Anti-cancer Radiology on (SURVIVAL) follow up", and "Anti-cancer Surgery on (SURVIVAL) follow up".

6.6 PHARMACOKINETIC ANALYSES

Calculations of pharmacokinetic parameters will be delivered separately.

6.7 PHARMACODYNAMICS ANALYSES

A pharmacodynamics report with raw and analyzed data will be provided separately.

6.8 OTHER ANALYSES

The methods for the summary and analysis of the BTK inhibition activity of zanubrutinib in PBMCs via BTK occupancy assay will be provided in a separate document.

The methods for the summary and analysis of the BTK inhibition activity of obinutuzumab in PBMCs via BTK occupancy assay will be provided in a separate document.

The methods for the summary and analysis of potential resistance biomarkers will be provided in a separate document.

7 Interim Analysis

No formal interim analyses are planned for this study. Data from the individual dose escalation cohorts in Part 1 of the study were reviewed by the study monitoring committee at the end of the DLT observation period for each cohort. No DLT was found in either regimen. Summaries and analyses of subsets of the study data were performed on a periodic basis for submission to professional meetings and for internal decision-making.

8 Changes in The Planned Analysis

This SAP provides more detail on the statistical methods than is provided in the protocol. The efficacy endpoints for combined Part 1 and Part 2 cohorts which were not defined in the protocol were added to the SAP.

9 References

Cheson, B.D., et al. Recommendations for Initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology,* 2014; 32(27): 3059–3068.

Cheson, B.D., et al. Novel Targeted Agents and the Need to Refine Clinical End Points in Chronic Lymphocytic Leukemia. *Journal of Clinical Oncology,* 2012; 30(23): 2820-2822.

Fleiss, J.L. *Statistical Methods for Rates and Proportions, Second Edition,* 1981, New York: John Wiley & Sons, Inc.

Hallek, B.D., 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): 5446–5456.

Owen, R.G., et.al. Response assessment in Waldenström Macroglobulinaemia: Update from the VIth International Workshop, *British Journal of Haematology,* 2013; 160(2): 171-176.

10 Appendix

10.1 Appendix A: Missing Data Imputation Rule

In general, missing or partial dates will not be imputed. The following rules will apply for the specific analysis and summary purposes mentioned below only.

A.1 Prior/Concomitant Medications/Procedures

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 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 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.

A.2 Adverse Events

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 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 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.

A.3 Deaths

In case only the day of a death date is missing, the death will be assumed to be on the 1st date of the month if the last date of subject known to be alive is earlier that the 1st date of the month, otherwise the death date will be assumed to be on 1 day after the last date of subject known to be alive.

A.4 New Anti-Cancer Therapy

If the start day of a new anti-cancer treatment, radiotherapy, or surgery is incomplete or missing, impute as follows:

- If only day is missing, then the imputed day will be the first day of the month.
- No imputation will be performed for all other types of missing dates.

A.5 Date of Diagnosis or Date of Progression to Any Prior Therapy

If an initial diagnosis date or disease progression date to any prior therapy is 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 a diagnosis date or progression date is completely missing, do not impute.

A.6 Prior Therapies, Radiotherapies, or Surgeries

If a prior therapy, radiotherapy, or surgery date is missing, impute as follows:

- If only day is missing, then set to the 15th of the month.
- No imputation will be performed for all other types of missing dates.

10.2 APPENDIX B: KEYWORD LIST OF IDENTIFYING COMPLIANCE-RELATED ZANUBRUTINIB DOSE INTERRUPTIONS

The following keywords will be used in the search of the "Dose Adjustment Reason" field (free-text) on the "BGB-3111 Administration" CRF when "Drug interrupted" was selected in the previous field in order to identify zanubrutinib interruptions due to compliance issues. Since the list was created by examining the real data, it may be modified until the final database lock.

- COMPLIANCE
- ERROR
- MISS
- MISSING
- MISSED
  - But if the words "MISS/MISSING/MISSED" and "ELECTIVE" are in the same phrase this is **not** a compliance issue and should not be included
  - But if the words "MISS/MISSING/MISSED" and "INFECTION" are in the same phrase this is **not** a compliance issue and should not be included
- SKIP
- SKIPPED
- FORGOT
- FORGOTTEN
- DID NOT TAKE
- DIDN'T TAKE
- NOT TAKEN
  - But if the words "DID NOT TAKE/DIDN'T TAKE/NOT TAKEN" and "CONSTIPATION" are in the same phrase this is **not** a compliance issue and should not be included
- ACCIDENTALLY TOOK
- RAN OUT
- RUN OUT
- RUNNING OUT
- SELF ADMINISTER
- SELF ADMINISTERED
- TRAVELING

- OUT OF TOWN

The following are to be picked out as compliance issues if they match exactly:

- PATIENT TOOK MORNING DOSE
- PATIENT ONLY TOOK MORNING DOSE
- PATIENT TOOK EVENING DOSE
- PATIENT ONLY TOOK EVENING DOSE