STATISTICAL ANALYSIS PLAN

Study Protocol Number	BGB-3111-110
Study Protocol Title	A Phase 1, Open Label, Multiple Dose, Dose Escalation and Expansion Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Zanubrutinib, in Combination With Lenalidomide, With or Without Rituximab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma
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Author: [redacted] Principle Statistician, GSDS	[redacted]

Approval

[redacted] Head of Global Statistics	[redacted]
[redacted] Chief Medical Officer	[redacted]
[redacted] Senior Physician, Clinical Development	[redacted]

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABC	Activated B-cell like
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the last measurable time points
BID	Twice daily
BOR	Best overall response
BTK	Bruton tyrosine kinase
C_{max}	Maximum observed plasma concentration
C_{max_ss}	Maximum observed plasma concentration at steady state
C_{trough}	Minimal drug concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
CI	Confidence interval
CL/F	Apparent clearance
CR	Complete response
CRF	Case report form
CRR	Complete response rate
CT	Computed tomography
CV%	Inter-subject variability
DLBCL	Diffuse large B cell lymphoma
DLT	Dose limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
GCB	Germinal-center B-cell
GEP	Gene expression profiling
IHC	Immunohistochemistry

Abbreviation	Definition
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred terms
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
QD	Once daily
R_{AUC}	Accumulation ratio of AUC
R_{Cmax}	Accumulation ratio of C_{max}
R_O	Accumulation ratio
RP2D	Recommended Phase 2 dose
R/R	Relapsed/refractory
SAE	Serious adverse events
SAP	Statistical analysis plan
SMC	Safety Monitoring Committee
SOC	System organ class
T_{max}	Time to maximum observed plasma concentration
TEAE	Treatment-emergent AE
TTR	Time to response
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the detailed plan for analysis of data in evaluation of safety and efficacy for the BGB-3111-110. This document is based on Protocol Amendment Version 2.0 dated 01 December 2020.

2. STUDY OVERVIEW

This is a phase 1, open label, multiple doses, dose escalation and expansion study of Bruton's Tyrosine Kinase (BTK) Inhibitor, zanubrutinib, in combination with lenalidomide in patients with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL). This study consists of two parts.

2.1. Part 1

Part 1 is the dose escalation portion, consisting of lenalidomide dose escalation with zanubrutinib fixed dose as the table below:

Table 1: Doses and schedules of interest in dose escalation

Dose Level	Zanubrutinib	Lenalidomide
Dose Level -1	160 mg BID	10 mg QD
Dose Level 1 (Starting dose)	160 mg BID	15 mg QD
Dose Level 2	160 mg BID	20 mg QD
Dose Level 3	160 mg BID	25 mg QD

BID=twice daily; QD=once daily

For dose escalation, 3+3 principles will be followed for the maximum tolerated doses (MTD) determination. The dose of zanubrutinib will remain fixed with up to 3 dose levels of lenalidomide to be explored according to Table 1. Zanubrutinib will be administered orally at 160 mg BID, while lenalidomide will be administered orally daily at the dose designated by dose levels in Table 1 on Days 1-21 of each 28-day cycle. Both zanubrutinib and lenalidomide will continue until disease progression (PD) or unacceptable toxicity.

The starting dose of lenalidomide will be 15 mg/day. The dose limiting toxicity (DLT) observation period is 28 days (1 cycle) of therapy followed by evaluation for toxicity on Cycle 2 Day 1, where the DLT is defined in Section 3.2.1.1 of the protocol. Further, define the MTD as the highest dose at which < 33 % of the patients enrolled at one dose level experience a DLT.

Enrollment will proceed as follows.

- If no DLT is observed during the DLT observation period in the initial three patients of a cohort (0/3), dose escalation to the next higher dose level cohort will occur.

- If one DLT is observed, three additional patients will be enrolled at the same dose level for a total of at least six patients. If no further DLTs are observed $(1/6)$, escalation to the next higher dose level cohort will occur.
- If two or more DLTs ($\geq 2/6$) are observed in patients, the MTD is considered to have been exceeded and no further patients will be enrolled at that dose.
- If there are two or more DLTs in Dose Level 1, Dose Level -1 will be enrolled.
- If all evaluated dose levels demonstrate an observed incidence of DLT in $< 33\%$ of patients, the MTD of lenalidomide in the combination has not been reached. At least six patients should be treated at the MTD or highest tested dose.
- If a patient experiences a DLT during the DLT observation period, the patient will discontinue treatment.
- The decision to proceed to the next dose level or an interim dose level will be made in a Dose Level Review Meeting by the Sponsor in conjunction with the investigators after careful consideration of all available safety and laboratory information. Safety data from patients on preceding cohorts that remain on continuous dosing will also be considered.
- According to study results and other relevant information, more additional patients, up to 12 patients, may be allowed to enroll to tested doses at or below MTD by Safety Monitoring Committee (SMC) to collect more safety data.

In the Dose Escalation Phase, if a patient is non-compliant with the prescribed therapy or ends treatment within the first cycle for reasons other than study drug(s) related toxicity, ie, withdraws consent, they will be replaced. Any patient that missed >4 doses of zanubrutinib or lenalidomide for reasons other than toxicity will be replaced.

Pharmacokinetics (PK) blood sampling will be performed at predose (0 hr), 0.5, 1, 2, 3, 4, 8hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentration.

After the PR2D of lenalidomide is defined, further enrollment into Part 2 will commence.

2.2. Part 2

Part 2 will be conducted as an open label, single arm, multicenter, expansion study with Simon's two-stage design (Simon, 1989). Eligible R/R DLBCL patients will receive zanubrutinib combined with lenalidomide. The dose of lenalidomide will be based upon the recommended the RP2D identified in Part 1. Both treatment medications will continue until PD or unacceptable toxicity.

PK blood sampling will be performed for 12 patients from the first stage enrollment at predose (0 hr), 0.5, 1, 2, 3, 4, 8 hr on Cycle 1 Day 1 and Cycle 1 Day 21 for measurement of plasma zanubrutinib and lenalidomide concentration.

During both parts, immunohistochemistry (IHC) and gene expression profiling (GEP) will be used to assess enrolled patients' status with respect to subtype of DLBCL. Subjects can be classified into germinal-center B-cell (GCB) or non-GCB like phenotype by IHC, and into the three subtypes: activated B-cell like (ABC), GCB and unclassified, by GEP.

3. STUDY OBJECTIVES

3.1. Part 1

3.1.1. Primary Objectives

- To determine the MTD and the RP2D of zanubrutinib in combination with lenalidomide, by dose escalation of lenalidomide in patients with R/R DLBCL.
- To determine the safety and tolerability of zanubrutinib in combination with lenalidomide, in patients with R/R DLBCL by dose escalating lenalidomide.

3.1.2. Secondary Objectives

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide in patients with R/R DLBCL as measured by overall response rate (ORR) assessed by investigator.
- To characterize the PK profiles of zanubrutinib and lenalidomide after single dose and at steady state when given in combination.
- To evaluate the efficacy, as measured by ORR, of zanubrutinib in combination with lenalidomide in different DLBCL subtypes.

3.1.3. Exploratory Objectives

- To evaluate the efficacy of zanubrutinib in combination with lenalidomide as measured by complete response rate (CRR), time to response (TTR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS), in patients with R/R DLBCL as well as in patients within different subtypes of R/R DLBCL.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes.
- To explore mechanisms of disease resistance.

3.2. Part 2

3.2.1. Primary Objectives

To evaluate the efficacy of zanubrutinib combined with lenalidomide in patients with R/R DLBCL as measured by ORR.

3.2.2. Secondary Objectives

- To evaluate the efficacy of zanubrutinib combined with lenalidomide, as measured by CRR, PFS, TTR and DOR.
- To determine the safety and tolerability of zanubrutinib combined with lenalidomide in patients with R/R DLBCL.
- To further characterize the PK profiles of zanubrutinib and lenalidomide after single dose and at steady state when given in combination.
- To evaluate the efficacy (ORR, CRR, TTR, PFS, and DOR) based on the DLBCL subtypes.

3.2.3. Exploratory Objectives

- To evaluate OS.
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes (eg, ORR, CRR, PFS, TTR, DOR and OS).
- To explore mechanisms of disease resistance.

4. STUDY ENDPOINTS

4.1. Part 1

4.1.1. Primary Endpoints

The primary endpoint is the safety of zanubrutinib combined with lenalidomide which will be assessed throughout the study by monitoring adverse events (AE) and serious AEs (SAE), per the NCI-CTCAE Version 5.0, physical examination and laboratory measurements, within the safety analysis set.

The RP2D of lenalidomide will be determined based on safety data.

4.1.2. Secondary Endpoints

Define the best overall response (BOR) as the best response recorded from the start of the combination therapy until data cut or start of new anticancer treatment.

The secondary endpoints are described as follows.

- ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification (Cheson, et al., 2014)
- PK evaluations, for zanubrutinib and lenalidomide, as appropriate and allowed by the data. For a single dose profile, the evaluations include but not limited to $AUC_{(0-t)}$, C_{max}, T_{max} and CL/F. Furthermore, for a steady state profile, the evaluations include but not limited to $AUC_{(0-t)}$, C_{max_ss} , T_{max}, C_{trough}, CL/F and Ro.
- Clinical outcomes, as measured by ORR, based on different subtypes (GCB and non-GCB classified by IHC, and ABC and GCB by GEP).

4.1.3. Exploratory Endpoints

The exploratory endpoints are the clinical outcomes and then by clinical/genetic risk factors and potential resistance biomarkers and mechanisms of resistance.

The clinical outcomes of interest are listed as follows.

- CRR, defined as the proportion of patients whose BORs are CR based on the Lugano classification (Cheson, et al., 2014).
- PFS, defined as the time from the documented date of treatment initiation to the documented date of PD, assessed based on the Lugano classification (Cheson, et al., 2014), or the date of death, whichever occurs earlier.
- DOR, defined as the time from the documented date of first response to the documented date of PD, assessed based on the Lugano classification (Cheson, et al., 2014), or the date of death, whichever occurs earlier.
- TTR, defined as the time from the documented date of treatment initiation to the documented date of first response.
- OS, defined as the time from the documented date of treatment initiation to the date of death from any cause.

4.2. Part 2

4.2.1. Primary Endpoints

ORR, defined as the proportion of patients whose BORs are either PR or CR based on the Lugano classification (Cheson, et al., 2014).

4.2.2. Secondary Endpoints

- Clinical outcomes of zanubrutinib combined with lenalidomide, including CRR, PFS, TTR and DOR, in the efficacy analysis set as well as the subgroups classified by IHC and by GEP.
- Safety and tolerability of zanubrutinib combined with lenalidomide will be assessed throughout the study by monitoring AEs and SAEs, per the NCI-CTCAE Version 5.0, physical examination and laboratory measurements.
- PK evaluations, for zanubrutinib and lenalidomide, as appropriate and allowed by the data, including but not limited to $AUC_{(0-t)}$, C_{max}, T_{max} and CL/F for a single dose profile and $AUC_{(0-t)}$, C_{max_ss}, T_{max}, C_{trough}, CL/F and Ro for a steady state profile.
- Clinical outcomes (eg, ORR, CRR, DOR, PFS, TTR) based on the GCB and non-GCB identified by IHC and ABC and GCB subtype identified by GEP.

4.2.3. Exploratory Endpoints

- OS.
- Clinical outcomes (ORR, CRR, PFS, TTR and DOR) by clinical/genetic risk factors.
- Potential resistance biomarkers and mechanisms of resistance.

5. SAMPLE SIZE CONSIDERATION

The number of dose levels to examine and the emerging toxicities of the combination therapy will determine the sample size. It is anticipated that approximately 27 patients in Part 1 and approximately 36 patients in Part 2 will be required. Under 10% dropout rate in Part2 by assumption, approximately 67 patients will be enrolled in total.

Sample size in Part 1 will depend on the number of dose levels to examine and the emerging toxicities of the combination therapy.

For Part 2, Simon's two-stage design will be used. The null hypothesis that the true response rate is 0.25 will be tested against a one-sided alternative. In the first stage, if there are 4 or fewer responses in the first 18 patients, the study will be terminated. The null hypothesis will be

rejected if 15 or more response are observed in 36 patients. This design yields a type I error rate of 0.025 and power of 96% when the true response rate is 0.55.

6. STATISTICAL METHODS

6.1. Analysis Sets

Safety analysis set is defined as all patients who are exposed to at least one dose of any medication within the combination therapy.

Efficacy analysis set is defined as all patients who are exposed to at least one dose medication with confirmed R/R DLBCL. Patients with no post-baseline response assessments will be treated as non-responders. It will be used as the primary analysis set for all the efficacy analyses.

Efficacy evaluable analysis set is defined as all patients who are exposed to at least one medication with confirmed R/R DLBCL and have at least one post-baseline response assessment unless discontinued treatment due to clinical progression or death prior to response assessment in the efficacy analysis set. It will be used for sensitivity analyses.

PK analysis set is defined as all patients who have at least one post dose plasma concentration collected without major protocol deviation affecting PK. It will be used for PK analysis.

Biomarker analysis set is defined as all the patients who is in a valid subtype of DLBCL classified by IHC or GEP and has at least one disease assessment after the initiation of treatment. It will be used for biomarker analysis.

6.2. Data Analysis General Consideration

6.2.1. Definitions and Computations

Definitions are described as follows.

- Study drugs are zanubrutinib, in combination with lenalidomide.
- Date of treatment initiation = Date of the first dose of any study drug in the treatment phase.
- Study days = Assessment date − Date of treatment initiation + 1 in days, if assessment conducted on or after the date of the treatment initiation; and Study days = Assessment date − Date of treatment initiation in days, if assessment conducted before the date of the treatment initiation. Note that there is no study day 0.
- Baseline = The last nonmissing value collected on or before the treatment initiation.

All calculations and analyses will be conducted using SAS® Enterprise Guide Version 7.15 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.
- 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'.
- 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 non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, descriptive statistics will include sample size, mean, standard deviation, median, 1st and 3rd quartiles and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages

6.2.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are described as follows.

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.

6.2.3.1. Impute partial dates for prior/concomitant medication/therapy/procedure

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

If start date of a medication/therapy/procedure 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/therapy/procedure 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 the imputed end date > death date/end of study, then set to death date/end of study, whichever occurs first.
- For records with CM.CMCAT='PREVIOUS SYSTEMIC THERAPY', if the imputed end date is on or after ADSL.TRTSDT then derive it as ADSL.TRTSDT - 1.

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

6.2.3.2. Impute partial dates for adverse events

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

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 the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute.

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, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date

with AE end date as final imputed AE start date

- If the imputed start date > death date, then set to death date

6.2.3.3. Impute partial dates related to disease history and prior therapy (drug, surgery/procedure, radiotherapy)

The following rules will be applied to impute partial dates such as initial diagnosis date, initial BCLC staging date, relapse date, therapy date (start/end date), or surgery date etc.

If start date of a disease history or prior therapy 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 the imputed start date > first dose date then set to first dose date – 1

If end date of a disease history or prior therapy 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 the imputed end date > first dose date, then set to first dose date -1

6.2.3.4. Impute partial dates for subsequent anti-cancer therapy (same rule applies to safety and efficacy flag)

If start date of subsequent anti-cancer therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 1st
- If only day is missing, then set to first day of the month
- If the subsequent anti-cancer therapy is collected from CRF “post-treatment discontinuation anti-cancer systemic therapy” or “post-treatment discontinuation anti-cancer procedure” page, and the imputed date is prior to the last dosing date, then set to last dosing date + 1

If stop date of 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 the imputed stop date > min (death date, study discontinuation date, data cutoff date), then set to min (death date, study discontinuation date, data cutoff date)
- The imputed stop date must be after or equal to the end date

If year of the start date/stop date is missing, do not impute.

6.2.4. Adjustments for Covariates

No adjustments for covariates are planned for primary and secondary analyses in this study, while baseline covariates may be included in the statistical models for exploratory analysis.

6.2.5. Multiple Comparisons/Multiplicity

Not applicable.

6.2.6. Data Integrity

Before pre-specified statistical analysis begins, the integrity of the data will be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' 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.

6.3. Subject Characteristics

Subject characteristics will be performed to the safety analysis sets of cohorts at each dose level in Part 1, the cohort in Part 2, and the pooling of cohorts at RP2D in Part 1 and Part 2 separately.

6.3.1. Subject Disposition

Number and percentage of enrolled patients will be summarized by categories, including treated, discontinued from treatment, remained on treatment, discontinued from study and remained in study. Primary reasons for discontinuation of each study drug and discontinuation of study will also be summarized in the same table. Moreover, study follow-up time (months) will be summarized by descriptive statistics. Lastly, survival status (alive, death, or lost to follow-up) at the cutoff date will be summarized using the data from the survival follow-ups.

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

6.3.2. Protocol Deviations

Important protocol deviation criteria will be established and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for all enrolled patients and 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. Continuous variables include age (years), height (cm), weight (kg), body mass index (kg/m^2) and vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature); categorical variables include sex, race, age group (< 60 vs. ≥ 60 years), Eastern Cooperative Oncology Group performance status, hepatitis B core antibody and hepatitis C virus antibody. A listing of demographic and other baseline characteristics will be provided.

6.3.4. Disease History and Characteristics

History of disease and characteristic, as recorded on the case report form (CRF), will be summarized using descriptive statistics. Continuous variables for disease history and characteristics include time from initial diagnosis of DLBCL to study entry (days); categorical variables include with or without prior transplantation (including autologous and allogeneic stem cell transplantation), with or without prior radiotherapy, IHC subtype obtained from central lab, GEP subtype obtained from central lab, EBER ISH, c-MYC/BCL2/BCL6 rearrangement or expression status, Epstein-Barr virus in situ hybridization, disease stage at entry, disease status (relapsed or refractory), bulky disease (> 7.5 cm vs. ≤ 7.5 cm), extra-nodal disease and bone marrow involvement. A listing of disease history will be provided.

6.3.5. Prior Anticancer Drug Therapies and Surgeries

Prior anti-cancer drug therapies, prior anti-cancer radiotherapy, and prior anti-cancer surgeries will be summarized in the safety analysis set. The variables include number of patients with any prior anti-cancer therapy, number of prior regimens, duration of last therapy for prior anti-cancer drug therapies and curative intent, time from the end of last surgery to study entry for prior surgeries. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

6.3.6. Prior and Concomitant Medications

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 last dose of zanubrutinib, lenalidomide, whichever occurs later.

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

The number and percentage of patients in safety analysis set reporting prior/concomitant medications will be summarized by the ATC medication class and the WHO DD preferred term (PT) by phase. A listing of prior and concomitant medications will be provided.

6.3.7. Medical History

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

6.4. Safety Analyses

The sponsor, leading investigator and maybe other investigators will establish a SMC for ongoing safety assessment throughout the study. The SMC charter will define the organization members and procedures. The SMC will evaluate safety data from Part 1 and decide the dose level for next group or if enroll more eligible patients, based on the safety data from the former dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed.

Patients will be evaluated for AEs (all grades, according to NCI-CTCAE Version 5.0) and serious adverse events (defined in the protocol). Patients who have an AE leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

All safety analysis will be performed to the safety analysis sets of cohorts at each dose level in Part 1, the cohort in Part 2, and the pooling of cohorts at RP2D in Part 1 and Part 2 separately, except for DLT, which will be performed to the safety analysis sets of cohorts in Part 1.

6.4.1. Extent of Exposure

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

- $\text{Duration of treatment of zanubrutinib} = \text{End date of zanubrutinib} - \text{Start date of zanubrutinib} + 1$ in days.

- Duration of treatment of lenalidomide = End date of lenalidomide − Start date of lenalidomide + 1 in days, where the end date of lenalidomide is the latter one of the last dose date of lenalidomide and the Day 28 of the last cycle of lenalidomide, or death date, whichever occurs earlier.
- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.
- Actual dose intensity (mg/day): defined as the total dose of a study drug received by a patient divided by the duration of treatment of the study drug.
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity is defined as the planned dose on study day 1 by a patient divided by the duration of exposure.
- Number (%) of patients with dose reductions
- Number (%) of patients with dose interruptions
- Number (%) of patients with dose modifications
- Reasons for dose reductions
- Reasons for dose interruptions

6.4.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 20.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A treatment-emergent AE (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib or lenalidomide (whichever comes later), or the start of a new anticancer therapy, whichever comes first. Worsening of an event to Grade 5 beyond day 30 after last dose of study drug is also considered a TEAE (if it is prior to new anticancer therapy start). Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

DLT events will be summarized by dose level in the dose escalation phase.

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to

death, TEAEs that led to treatment discontinuation, TEAEs that led to dose reduction, TEAEs that led to dose interruption, zanubrutinib-related TEAEs, lenalidomide-related TEAEs will be provided. Treatment-related AEs include those events considered by the investigator to be probably related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with treatment-emergent SAEs, zanubrutinib-related TEAEs, lenalidomide-related TEAEs, TEAEs with grade 3 or above, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized by SOC and PT. TEAEs with grade 3 or above will also be summarized by PT in descending order.

Patient data listings of TEAE, treatment-emergent SAEs, zanubrutinib-related TEAEs, lenalidomide-related TEAEs, TEAEs with grade 3 or above, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided.

All deaths and causes of death will be summarized by cohorts and by total including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

Summaries including all TEAEs, AEs worsened after the treatment-emergent (TE) period and/or AE started after the TE period but determined to be treatment-related will also be provided.

6.4.3. Laboratory Analyses

Clinical laboratory (ie, hematology, serum chemistry, coagulation, urinalysis, serum immunoglobins, hepatitis serologies, and thyroid function) values will be evaluated for each laboratory parameter by patient. The laboratory parameters of interest are summarized in Table 2. Abnormal laboratory values will be flagged and identified as those outside the normal range. Reference ranges for laboratory parameters will be included in the clinical study report for the protocol.

Laboratory parameters and their changes from baseline will be summarized using descriptive statistics by visit. Laboratory parameters that are graded in NCI-CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to worst post-baseline grades in both high and low directions.

A summary of patients with a change of 2 or more toxicity grade compared to baseline and patients with postbaseline toxicity grade of 3 or more in both high and low directions will be provided for laboratory parameters of interest. Listings of selected laboratory parameters will be provided.

Table 2: Laboratory parameters of interest (including but not limited to)

Hematology		Serum Chemistry		Coagulation	Serum Immunoglobulins
hemoglobin	lymphocytes	alanine aminotransferase	albumin	PT	IgG
neutrophils	platelets	alkaline phosphatase	aspartate aminotransferase	aPTT	IgM
white blood cells	Hematocrit	calcium	creatinine		IgA
Red Blood Cell	Basophils	glucose	potassium		
Monocytes	Eosinophils	sodium	total bilirubin		
		uric acid	lactate dehydrogenase		

6.4.4. Vital Signs

Vital sign parameters, including systolic and diastolic blood pressure, pulse rate, temperature, and weight, and their change from baseline will be summarized using descriptive statistics by visit. Patient data listings of vital signs will be provided.

6.4.5. ECOG performance status

A shift table from baseline to worst post-baseline in eastern cooperative oncology group performance score will be summarized. Eastern cooperative oncology group status will be summarized by visit.

6.4.6. Electrocardiograms

Actual value and change from baseline for the electrocardiogram parameters (including heart rate, QT interval and QTcF interval) will be summarized. If triplicate readings are recorded, the average of the readings for the visit will be used for the summary.

The number and percentage of patients satisfying the following QTcF conditions at any time postbaseline will be summarized:

- > 480 and ≤ 500, or > 500 msec
- ≤ 30 msec maximum increase from baseline, > 30 and ≤ 60 msec maximum increase from baseline, or > 60 msec maximum increase from baseline

Patient data listings of electrocardiogram will be provided.

6.5. Efficacy Analyses

The efficacy analysis will be performed on the efficacy analysis set of cohorts at each dose level in Part 1, the cohort in Part 2, and the pooling of cohorts at RP2D in Part 1 and Part 2 separately unless otherwise specified in this section.

6.5.1. Hypothesis Test

No hypothesis testing will be performed for Part 1.

For Part 2, the ORR with the combination therapy is estimated as 55% in the overall R/R DLBCL population, which is deemed a clinical meaningful improvement. Simon's two-stage design (Simon, 1989) is based on the following hypothesis testing problem

$$H_0: \mathrm{ORR} = 25\% \quad \text{vs.} \quad H_a: \mathrm{ORR} \geq 25\%$$

in the efficacy analysis set of the cohort in Part 2. If the obtained one-sided p-value is less than 0.025, it will be concluded that the combination therapy statistically significantly increases ORR compared to the historical control.

As stated in Section 2.2, if no more than 4 responses are observed within the first 18 patients in Part 2, the study will be stopped.

6.5.2. Efficacy Analysis for Response Rates

The response rates of interest are calculated as follows.

$$\text{ORR} = \text{Number of patients whose BORs are PR or CR} / \text{Number of patinets in the efficacy analysis set}.$$

- $$\text{CRR} = \text{Number of patients whose BORs are CR} / \text{Number of patinets in the efficacy analysis set}.$$

ORR will be directly estimated by the proportion of patients whose BORs are either PR or CR based on the Lugano classification (Cheson, et al., 2014). CRR will be estimated in a similar way by replace the patients whose BORs are either PR or CR by those whose BORs are CR. The precision of the estimators will be assessed by two-sides Clopper-Pearson 95% confidence intervals (CI).

For analysis of disease response, BOR will be summarized as a categorical variable (CR, PR, stable disease, PD, not evaluable and not accessed), while study follow-up time as a continuous variable using descriptive statistics. Furthermore, ORR and CRR and their 95% CIs will also be presented in the table. A listing of BOR will be provided.

Same analysis will be performed on the efficacy evaluable analysis set for sensitivity analysis.

6.5.3. Efficacy Analysis for Time to Event Endpoints

PFS is defined as the time from the starting date of the combination therapy to the date of first documentation of disease progression or death, whichever occurs first. Patients who do not have disease progression will be censored at their last valid tumor assessment.

Kaplan-Meier method will be used to estimate progression event-free curves and corresponding quantiles (including the median). A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. The PFS at 6 and 12 months, defined as the percentages of patients in the analysis set who remain alive and progression-free at the specified timepoints, will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula.

The PFS censoring rule will follow FDA Guidance for Industry Clinical Study Endpoints for the Approval of Cancer Drugs and Biologics (2018) in Appendix A.

TTR is defined as time from the starting date of combination therapy to the date the response criteria are first met and will be summarized among responders.

DOR is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. Patients who do not have disease progression will be censored at their last valid assessment.

OS is defined as the time from the starting date of the combination therapy to the date of death due to any reason. Patients who are known to be alive as of their last known status will be censored at their date of last contact.

Time to event endpoints (DOR, TTR and OS) will be similarly analyzed using the Kaplan-Meier method as described above for PFS. The Kaplan-Meier estimates of TTR, DOR and OS will be plotted over time.

6.5.4. Subgroup Analyses

Overall response of patients in RP2Dwill be summarized descriptively in the specified subgroups: sex, age group (<60 vs ≥=60), disease stage, disease status (relapsed vs. refractory), ECOG-PS (0 vs. ≥1), number of prior lines of therapy (1, 2, >=3), , bulky disease (>7.5 cm), extra nodal site (<=1 vs >1). Within group values (rates or means/medians) will be presented in forest plots.

6.6. Pharmacokinetic Analyses

The following analysis plan provides the framework for the summarization of the PK data from study BGB-3111-110. The objective is to assess plasma zanubrutinib and lenalidomide PK profile in different parts. The PK analyses will be performed on PK analysis set. Plasma zanubrutinib and lenalidomide concentration time data will be summarized and displayed in both tabular and graphical form. Individual and mean plasma concentration versus time data will be tabulated and plotted by dose level. Additional PK analyses may be conducted if deemed necessary and will be described in a separate analysis plan.

6.6.1. Calculation of Pharmacokinetic Parameters

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized by treatment and part using descriptive statistics. PK parameters will be estimated based on non-compartmental analysis methods and will be computed using Phoenix WinNonlin® Version 8.0. or higher.

Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

The PK parameter estimates for a single dose (Cycle 1 Day 1) profile includes but is not limited to the following.

Parameter (Units)	Definition	Method of Determination
AUC_{last} (ng*h/mL)	Area under the concentration-time curve from time zero to time of last quantifiable concentration	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_t (ng*h/mL)	Area under the concentration-time curve from time zero to time t (8 hour)	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{inf} (ng*h/mL)	Area under the concentration-time curve from time zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (ng/mL)	Maximum observed concentration	Reported value
T_{max} (h)	Time of the maximum observed concentration	Actual elapsed time for observed C_{max}
T_{last} (h)	Time of the last quantifiable concentration	Actual elapsed time for observed the last quantifiable concentration
$t_{1/2}$ (h)	Apparent terminal elimination half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL/F (L/h)	Apparent drug clearance	Calculated as Dose/(AUC_{inf}*F), where F is the fraction of dose absorbed
V_z/F (L)	Apparent volume	Calculated as CL/F/λ_z, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
$\%AUC_{extrap}$ (%)	Percentage of AUC due to extrapolation from the last quantifiable concentration to infinity	Calculated as (AUC_{inf}-AUC_{last})/AUC_{inf}*100

The PK parameter estimates at steady state (Cycle 1 Day 21) included but not limited to the following.

Parameter (Units)	Definition	Method of Determination
AUC_{last} (ng*h/mL)	Area under the concentration-time curve from time zero to time of last quantifiable concentration	Calculated using the linear up/log down variant of the trapezoidal rule

AUC_t (ng*h/mL)	Area under the concentration-time curve from time zero to time t (8 hour)	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{tau} (ng*h/mL)	Area under the concentration-time curve during a dosing interval (tau)	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (ng/mL)	Maximum observed concentration	Reported value
C_{trough} (ng/mL)	Observed concentration at the end of dosing interval	Reported value
T_{max} (h)	Time of the maximum observed concentration	Actual elapsed time for observed C_{max}
T_{last} (h)	Time of the last quantifiable concentration	Actual elapsed time for observed the last quantifiable concentration
$t_{1/2}$ (h)	Apparent terminal elimination half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL_{ss}/F (L/h)	Apparent drug clearance	Calculated as Dose/(AUC_{tau}*F), where F is the fraction of dose absorbed
V_z/F (L)	Apparent volume	Calculated as $CL_{ss}/F/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
AR_{AUC}	Accumulation ratio of AUC	AUC_t on Day 21 of Cycle 1/AUC_t on Day 1 of Cycle 1
AR_{Cmax}	Accumulation ratio of C_{max}	C_{max} on Day 21 of Cycle 1/C_{max} on Day 1 of Cycle 1

The parameters C_{max}, T_{max} and T_{last} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, T_{max} will be assigned to the first occurrence of C_{max}.

6.6.2. Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. The concentration and time data of zanubrutinib and lenalidomide will be listed individually and summarized by part and dose level using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.
- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term “BLQ” with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of

descriptive statistics. BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).

- If a concentration at a given time point is missing, it shall be reported as a missing value. If missing data are not identified in the bioanalytical source (i.e., the record is missing), the reporting convention of "NS" shall be utilized.
- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and geometric CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

6.6.3. Plots of Pharmacokinetic Plasma Concentrations

For zanubrutinib and lenalidomide, plasma concentration versus time data will be plotted individually and summarized graphically using arithmetic mean (±SD) plots by treatment group, respectively. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on linear scale but not shown on log-linear scale.

6.6.4. Reporting of PK Parameters for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters except t_{max} and $t_{1/2}$ should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%.
- For in-text tables, geometric mean (geometric CV%) will be the default method of reporting PK parameters. t_{max} should be presented as median, range (minimum, maximum), when presenting the summary statistics. $t_{1/2}$ should be presented as geometric mean, range (minimum, maximum).
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.
- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g. AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.
- In this scenario, for reporting PK parameters such as AUC and C_{max}, the following guidance is provided for rounding:

  - If the numerical value is below 100 then one decimal place may be used e.g. 0.1 or 99.9.

  - For values ranging from >100, whole numbers should be used e.g. 100 or 9999.

- If > 10,000 the clinical pharmacologist may decide on changing units e.g. from ng/ml to μg /ml.

- For reporting times e.g. for t_{max} or $t_{1/2}$, if <1 hour use 2 decimals; time up to 24 hour should be reported to one decimal place e.g. 23.5 hour, time >24 hour should be rounded to nearest whole number e.g. 105 hr.

6.6.5. Accumulation Ratio Analysis

Accumulation ratio is defined as the ratio of plasma exposure (AUC, C_{max}) at steady state (Day 21) to the plasma exposure after the first dose (Day 1) of lenalidomide. Accumulation ratio can be presented in the subject level by

$$\frac{\text{Plasma Exposure}_{Day\ 21}}{\text{Plasma Exposure}_{Day\ 1}}$$

Accumulation ratio for lenalidomide of C_{max} and AUC_t may be assessed using linear mixed effects models, including dose, day, and dose-day interaction as the fixed effect and a subject-level random effect.

$$\log(\text{PK parameter}) = \beta_0 + \beta_1 \times \text{dose} + \beta_2 \times \text{day} + \beta_3 \times \text{dose} * \text{day} + \beta_4 \times \text{subject} + \varepsilon$$

where subject is a subject-level random effect. The categorical variable, day, distinguishes daily plasma exposure on day 1 and plasma exposure on Day 21.

For each dose, the estimate of accumulation ratio will be obtained by applying an exponential function on the difference of least square (LS) means of $\log(PK_{Day\ 21})$ and $\log(PK_{Day\ 1})$. Similarly, a 95% CI for the accumulation ratio will be obtained by applying the exponential function on the 95% CI for the mean of $\log(PK_{Day\ 21})$ - $\log(PK_{Day\ 1})$. Provided below is the pseudo SAS code for running the model:

```
proc mixed data= pkdata;
    class dose day (ref=day1) subject;
   model logpk = dose day dose*day / solution;
   random subject;
   lsmeans dose*day/slice=dose diff cl;
   ods output lsmeans=lsmeans diffs=diffs;;
run;
```

6.7. Biomarker Analyses

Biomarker analysis will be performed on the biomarker analysis sets of cohorts at each dose level in Part 1, the cohort in Part 2, and the pooling of cohorts at RP2D in Part 1 and Part 2 separately.

6.7.1. Predictive Biomarkers

Clinical outcomes (ORR, CRR, PFS, TTR, OS or DOR) will be analyzed in subgroups identified by these biomarker subtypes (ie, GCB and non-GCB classified by IHC, and GCB and ABC by GEP) using the same methods described in Section 6.5.

A supportive analysis is based on patients with a valid subtype classification measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response. Similar analyses described above will also be used.

Other statistical models (ie, logistic model for ORR, or Cox proportional hazards model for time to event endpoints) may be fitted with biomarker subtype index as covariate to explore its correlation with the clinical outcomes.

Exploratory analyses of other predictive biomarkers or clinical/genetic risk factors such as *Ki67*, Epstein-Barr virus infection status, *MYC/BCL2/BCL6* rearrangement status, genomic alteration status, tumor infiltrating lymphocytes levels, International Prognostic Index, etc. will be conducted similarly if data is available.

6.7.2. Other Biomarkers

For patients with paired tumor biopsies or blood, correlation between changes in the tumor tissues or peripheral blood, including but not limited to BTK pathway gene expression, tumor infiltrating lymphocytes levels, RNA expression and DNA mutational profiling, immune cell and cytokine profiling, ctDNA levels, and tumor response will be analyzed to identify potential pharmacodynamics and monitoring biomarkers.

When deemed necessary, correlation analyses described for the predictive biomarkers will also be performed for these pharmacodynamic and monitoring biomarkers vs. clinical outcomes (ORR, CRR, PFS, TTR and DOR). These biomarkers may be treated as continuous and/or categorical variables (if suitable threshold can be identified) in these analyses.

Tumor biopsy and blood samples taken at PD or response during the study will be used to identify potential resistance biomarkers and mechanisms. Similar analyses described for above

monitoring biomarker will also be performed for these resistance biomarkers, by replacing the efficacy endpoint of the response status with progression status.

7. INTERIM ANALYSIS

The interim analysis will be built based on the Simon's two-stage design for the cohort in Part 2; see Section 6.5.1 for details.

8. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9. REFERENCES

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Greenwood, M. (1926). The natural duration of cancer. *Public health and medical patients, 33*, 1-26.

Schemper, M., & Smith, T. L. (1996). A note on quantifying follow-up in studies of failure time. *Controlled Clinical Trials, 17*(4), 343-346.

Simon, R. (1989). Optimal Two-stage Design for Phase II Clinical Trials. *Controlled Clinical Trials, 10*, 1-10.

10. APPENDIX A: HANDELING OF CENSORING TIME TO EVENT DATA

The censoring rule for PFS will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research, 2018); see the following table. And this censoring rule will also apply to the other time to event data (DOR).

Table 4: Censoring rules for PFS

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessment	Date of treatment initiation	Censored
2	Progression documented on scheduled visit or between scheduled visit	Date of first disease assessment showing with documented PD	Progressed
3	Alive without documented PD at the time of data cut-off or withdrawal from the study (including lost-to-follow-up without PD)	Date of last disease assessment	Censored
4	New anticancer treatment started before documented PD or death	Date of last disease assessment prior to or on date of new anticancer treatment	Censored
5	Death before first disease assessment	Date of death	Progressed
6	Death or progression after more than one missed scheduled disease assessment	Date of last disease assessment without documented PD before missed disease assessment	Censored