STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-207
Study Protocol Title:	A Phase 2, Single arm, Multicenter, Open-label Study of Bruton's Tyrosine Kinase (BTK) inhibitor BGB-3111 in subjects with relapsed/refractory non-GCB type Diffuse Large B cell lymphoma
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	Adverse events
AESIs	Treatment-emergent adverse events of special interest
ADI	Actual dose intensity
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BOR	Best overall response
BP	Blood pressure
BTK	Bruton's Tyrosine Kinase
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLBCL	Diffuse Large B cell Lymphoma
DOR	Duration of response
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiograms
ECOG-PS	Eastern Cooperative Oncology Group performance status

eCRF	Electronic case report form
EOT	End of treatment
FDA	Food and Drug Administration
GI	Gastrointestinal
IWG	International Working Group
LDH	Lactate dehydrogenase
LDi	Longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
non-GCB	non-Germinal Center B cell type
NR	No response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease/disease progression
PET	Positron Emission Tomography
PFS	Progression free survival
PO	Per os (orally)
PR	Partial response
PT	Preferred term
RDI	Relative dose intensity
SAEs	Serious adverse events
SAP	Statistical analysis plan

SAS	Safety Analysis Set
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
TBL	Total bilirubin
TEAEs	Treatment-emergent adverse events
TTR	Time to response
ULN	upper limit of normal
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary
zanubrutinib	BGB-3111

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study BGB-3111-207.The focus of this SAP is for the planned analysis specified in the study protocol. The plan is written in accordance with the protocol version 2.0 dated 16 April 2018.

The analysis details for Biomarker analyses are not described within this SAP.

2 STUDY OVERVIEW

This is a single-arm, open-label, multi-center Phase 2 study in subjects with histologically documented non-Germinal Center B cell type Diffuse Large B cell Lymphoma (non-GCB DLBCL) who have relapsed after ≥ 1 prior treatment regimen including rituximab(s), patients also have to be ineligible for intensive chemotherapy and bone marrow transplantation. The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase of up to 2 years, and a follow-up phase (30 days), at the end of which if the patient is still benefiting from therapy, will be allowed to join the long-term extension study.

Up to approximately 40 subjects will be enrolled. The primary efficacy analysis will be conducted no later than 12 months after the last subject received the first dose of study drug. Tumor response will be assessed by investigator review according to 2014 International Working Group (IWG) in Non-Hodgkin's Lymphoma (NHL) (Cheson et al 2014) (Appendix 2). Patient will receive a positron emission tomography (PET) and contrast computed tomography (CT) at screening, after 12 and 24 weeks of therapy, and at suspected complete remission. Contrast CT alone will be performed at weeks 36, 48, and thereafter, once every 16 weeks. Response will be assessed based on radiological evaluations. Complete responses should be confirmed by PET and contrast CT in all subjects, by endoscopy for any subjects with a documented history of gastrointestinal involvement, and by bone marrow biopsy in these subjects with bone marrow tumor involvement prior to study drug. Bone marrow biopsy has to be performed at screening.

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

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

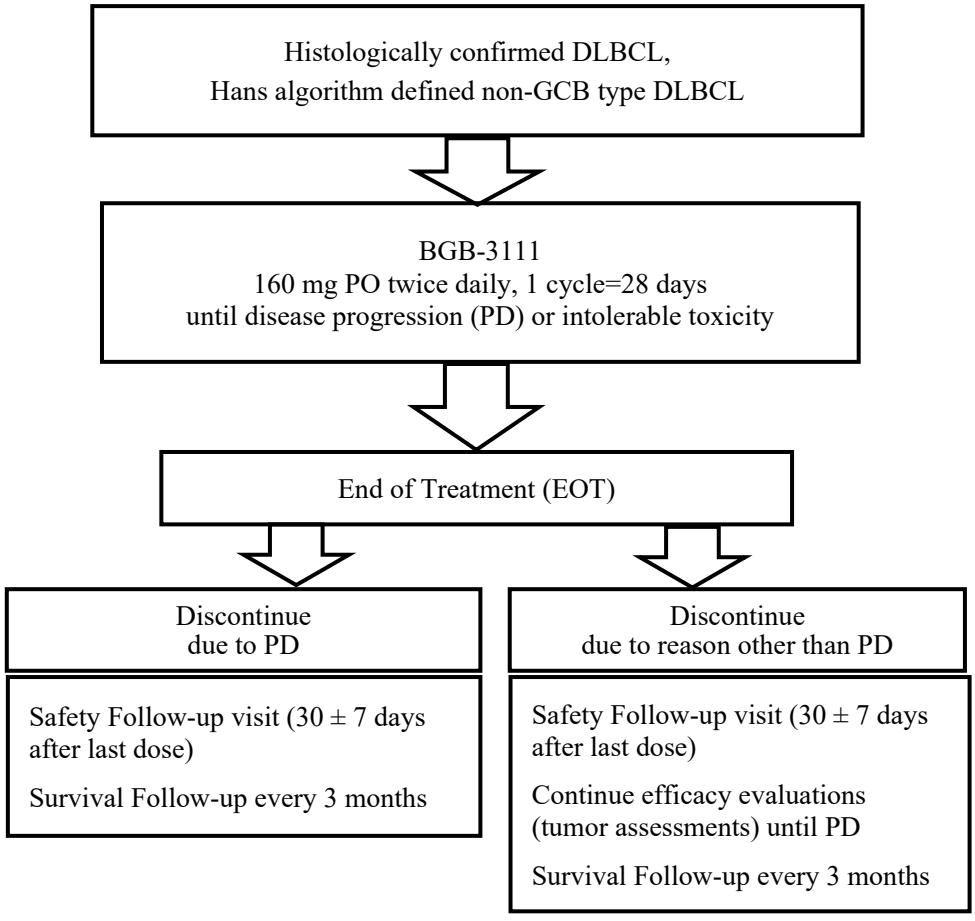
Treatment phase: Subjects will receive the first dose of zanubrutinib at Cycle 1 Day 1. All subjects in the study will be treated with 160 mg, administered orally (PO) twice daily (BID), and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal

of consent, or the study is terminated by the sponsor for final analysis. At the time of final analysis, subjects who remain on treatment will be considered for participation in the extension study when eligible. A treatment cycle consists of 28 days.

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

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

Figure 1 Schema for Study BGB-3111-207



3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the efficacy of zanubrutinib at a dose of 160 mg orally (PO) twice daily (BID), in subjects with relapsed or refractory non-GCB DLBCL as assessed by investigator review using the overall response rate according to the 2014 International Working Group in NHL criteria (Cheson et al 2014).

3.2 SECONDARY OBJECTIVES

- To evaluate the efficacy of zanubrutinib by investigator as measured by progression free survival (PFS).
- To evaluate the efficacy of zanubrutinib by investigator as measured by duration of response (DOR).
- To evaluate the efficacy of zanubrutinib by investigator as measured by time to response (TTR).
- To evaluate the safety and tolerability of zanubrutinib at a dose of 160 mg PO BID in subjects with relapsed or refractory non-GCB type DLBCL.

3.3 EXPLORATORY OBJECTIVES

- [redacted]

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

- The primary endpoint of the study is the rate of overall response, defined as the achievement of either a partial response (PR) or complete response (CR) by investigator review according to the 2014 modification of the International Working Group on NHL Criteria (Cheson et al 2014) (Appendix 2) at any time on study drug.

4.2 SECONDARY ENDPOINTS

Efficacy (using response assessment as determined by investigator):

- Progression free survival (PFS): defined as time from first dose of zanubrutinib until first documentation of progression (by IWG on NHL criteria) or death, whichever comes first.
- Duration of response (DOR) is defined as the time from the date that the response (PR or CR) criteria are first met to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.

- Time to response (TTR) is defined as the time from first dose of zanubrutinib to documentation of a response.

Safety:

- To evaluate the safety and tolerability of zanubrutinib, as defined by:
  - The incidence and severity of treatment-emergent adverse events (TEAEs), SAEs and treatment-related AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE v4.03).
  - The incidence, severity, timing, and causation of adverse events leading to study drug discontinuation.

4.3 EXPLORATORY ENDPOINTS

- [redacted]
- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

Approximately 40 subjects will be enrolled.

The sample size calculation was based on the level of precision of the estimated ORR. Assuming an ORR of 35%, the 95% exact confidence interval will be 20.6% to 51.7%.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

The Safety Analysis Set (SAS) includes all subjects who received any dose of zanubrutinib. It will be the population for the efficacy and safety analyses.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

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

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

Treatment duration: The treatment duration will be calculated as (end date of the latest exposure of study drug – date of first dose of study drug + 1).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the administration of the first dose of study drug.

All calculations and analyses will be conducted using SAS version 9.4 or higher.

6.2.2 Conventions

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

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, 25 percentile (Q1), 75 percentile (Q3), and range (minimum and maximum).
- For categorical 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 the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events, prior/concomitant medications/procedures, initial diagnosis date or most recent progression relapse date as provided in Appendix 1.

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

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

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

If the start day of a subsequent anti-cancer therapy is missing, it will be assumed to be the first day of the month if the end of treatment date is earlier. If the end of treatment date is later than the first day of the month, then the start date of subsequent anti-cancer therapy will be assumed to be the end of treatment date plus 1 day.

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

If both day and month of death date are missing, the death will be assumed to be on the first day of January if the last known alive date is earlier. If the last know alive date is later than the first day of January, then the death date will be assumed to be the last known alive date plus 1 day.

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

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

6.2.4 Handling of Treatment Cycles

A treatment cycle consists of 28 days. The following cycles will not be reset if the planned visit did not occur due to certain reason or there is dose held in current treatment cycle.

6.2.5 Adjustment for Covariates

No adjustments for covariates are planned for primary and secondary analyses in the study.

6.2.6 Multiplicity Adjustment

Not applicable.

6.2.7 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 each patient's 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 number (percentage) of subjects enrolled, treated, discontinued from study drugs and discontinued from the study will be summarized in the safety analysis set. The primary reason for end of treatment (study drug discontinuation) and end of study will be summarized by categories in the electronic case report form (eCRF).

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

Survival status (alive, death, or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

6.3.2 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented. Major protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set. Continuous variables include age, height and weight; categorical variables include sex, race, age group (< 65 vs. ≥ 65 years), Eastern Cooperative Oncology Group performance status (ECOG-PS), HBcAb, HBV DNA and HCV antibody. A listing of demographic and other baseline characteristics will be provided.

6.3.4 Disease History

The number (percentage) of subjects reporting a history of disease and characteristic, as recorded on the CRF, will be summarized in the safety analysis set. Disease characteristics include time since initial diagnosis of non-GCB DLBCL, disease status at study entry (Relapsed vs. Refractory), time from most recent progression relapse, disease stage at study entry, extra-nodal disease, international prognostic index (IPI) at study entry, bulky disease (defined as the longest diameter (LDi) of any target lesion > 7.5 cm), confirmed GI involvement and baseline bone marrow involvement, elevated lactate dehydrogenase (LDH) at baseline, spleen enlargement, liver enlargement and B-symptoms (defined as unexplained weight loss > 10% over previous 6 months or fever (> 38 ℃) or drenching night sweats). A listing of disease history will be provided.

6.3.5 Prior Anti-Cancer Drug Therapies and Surgeries

The number of prior lines of therapy, duration of last prior therapy, best response for last prior therapy, time (months) from the end of last prior therapy to first dose of study drug, number (%) of patients with prior anti-cancer radiotherapy will be summarized in the safety analysis set. 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 and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO DD) drug codes version September 2018 (B3 format) and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class level 2 and WHO DD preferred name in the safety analysis set. 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. 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 22.0. The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety analysis set. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

Analysis of efficacy endpoints will be conducted in the safety analysis set with the exception of DOR which will be summarized for responders only.

6.4.1 Primary Efficacy Endpoints

Overall Response Rate (ORR)

The primary efficacy endpoint of the study is ORR, defined as the proportion of subjects achieving a best overall response of CR or PR determined by investigator review using the 2014 International Working Group in NHL criteria (Appendix 2).

The ORR in this study is estimated as 35%. Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate. No hypothesis testing will be done.

Best overall response (BOR) is defined as the best response recorded from the start of zanubrutinib until data cut or start of new anti-neoplastic treatment. Patients with no post-baseline response assessment (due to any reason) will be considered as non-responders. The number and proportion of patients who achieved each of the response categories (CR, PR, stable disease/no response [SD/NR], and PD) will be summarized. The corresponding Clopper-Pearson 95% CI for CR rate and PR rate will also be presented.

The primary efficacy analysis will be conducted no later than 12 months after the first dose of the last patient and will be based on the safety analysis set.

6.4.2 Secondary Efficacy Endpoints

Progression Free Survival (PFS)

PFS is defined as the time (in months) from the first dose date of zanubrutinib to the earlier date of disease progression or death due to any cause.

PFS = (The earlier of disease progression or death date –first dose date +1) / 30.4375

PFS will be based on investigator's assessment. The distribution of PFS, including median PFS and PFS rates at selected timepoints such as 3, 6 and 12 months will be summarized descriptively using the Kaplan-Meier method. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time. Two-sided 95% CIs of median and other quantiles, if

estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982). The corresponding 95% CIs for PFS rates at selected timepoints will also be generated by using Greenwood's formula (Kalbfleisch and Prentice, 1980). Median of the follow-up time for PFS will be estimated by reverse Kaplan-Meier method (Schemper and Smith, 1996).

The PFS censoring rule will follow Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)" and be provided in Table 1.

Note that the frequency of disease assessments is every 12 weeks in the first 48 weeks and every 16 weeks thereafter. Therefore, missing more than one disease assessment will be interpreted as gaps longer than 24 weeks in the first 48 weeks or gaps longer than 32 weeks thereafter for censoring purposes of PFS.

Table 1 Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessments	Date of the first dose	Censored
2	Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
3	Alive without documented disease progression at the time of data cut-off or withdrawal from study (including lost-to-follow-up without disease progression)	Date of last disease assessment	Censored
4	New anticancer treatment started before documented disease progression or death	Date of last disease assessment prior to 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 disease progression before missed tumor assessments	Censored

Duration of Response (DOR)

DOR for responders (CR or PR) 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 for any cause (whichever occurs earlier). Censoring rule for DOR will follow PFS censoring rule. Kaplan-Meier curve will be used to estimate median time and 95% confidence interval for duration of response.

DOR will be based on investigator's assessment.

Time to response (TTR)

TTR for responders (CR or PR) is defined as the time interval between the first dose date of zanubrutinib to the date the response criteria are first met. TTR will be summarized by sample

statistics such as mean, median and standard deviation for responders only. TTR will be based on investigator's assessments.

6.4.3 Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: Sex (male vs female), age group (< 65 vs. ≥65 years), disease stage at study entry (Stage I/II vs. Stage III/ IV), ECOG-PS (0 vs. ≥1), IPI (low, low-intermediate, high-intermediate, high), bulky disease (LDi ≤ 7.5 vs. LDi > 7.5 cm), baseline bone marrow involvement (yes vs. no), baseline extra-nodal disease (yes vs. no), elevated LDH at baseline (yes vs. no), number of prior lines of therapy (1 vs. ≥2), prior rituximab containing therapy (yes vs. no), prior autologous stem cell transplantation (yes vs. no), prior Hyper CVAD use (yes vs. no) and MYD88/CD79B mutation ($MYD88^{L265P}$&$CD79B^{Mut}$ vs. others). Within group values (rates for ORR or medians for PFS) will be presented in forest plots.

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

6.4.4 Exploratory Efficacy Endpoints

[redacted]

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis set. The study will set up a Safety Monitoring Committee (SMC). The SMC will monitor safety data according to the SMC charter (Appendix 3) periodically throughout the study.

Safety and tolerability will be assessed, where applicable, by summarizing the incidence, severity, and causation of all TEAEs graded by NCI CTCAE v4.03.

Laboratory values (hematology, clinical chemistry and urinalysis), vital signs and ECGs findings, and the change from baseline values will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values will be flagged.

6.5.1 Extent of Exposure

Extent of exposure to study drug will be summarized descriptively with respect to the following:

- Duration of exposure (months): defined as the duration (months) from the date of the first dose to the last dose of the study drug.
- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.
- Total dose received per subject (mg): defined as the cumulative dose of the study drug during the treatment period of the study
- Actual dose intensity (ADI, mg/day): defined as the total dose (mg) received by a subject divided by the treatment duration (days)
- Relative dose intensity (RDI, %): defined as the ratio of the actual dose intensity (mg/day) and the planned starting dose intensity (mg/day).

The number (percentage) of patients requiring dose reduction and dose interruption due to AEs, and patients with dose missing will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 20.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

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

An overview table, including the incidence of and the number of subjects with TEAEs, serious TEAEs, TEAEs with grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification (including dose reduction and dose interruption) and all above TEAEs that were treatment-related will be provided. Treatment-related AEs include those events considered by the investigator to be related, probably related, possibly related and unlikely related to study treatment or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

The number (percentage) of subjects with all TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs with grade 3 or above, treatment-related TEAEs with

grade 3 or above, and TEAEs that led to treatment discontinuation, dose modification (reduction or interruption) will be summarized by SOC, PT and maximum severity. TEAEs and treatment-related TEAEs that led to death will be summarized by SOC and PT. All TEAEs, serious TEAE, TEAEs with grade 3 or above and treatment-related TEAEs will also be summarized by PT in descending order.

TEAEs of special interest (AESIs) are TEAEs known to be associated with ibrutinib and other BTK inhibitors and thought to be a class effect. The events and search terms for AESIs are shown in Table 2. The categories of AESIs are subject to change if warranted to better represent the safety of zanubrutinib before database lock.

Table 2: Adverse Events of Special Interest

AESI	Search Criteria
Hemorrhage	Hemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage	Major hemorrhage is defined as Subdural haematoma PT, Subdural haemorrhage PT and all Hemorrhage PT if AE SOC is 'Nervous system disorders' or serious or grade 3 and above Hemorrhage PT if AE SOC is not 'Nervous system disorders'
Atrial fibrillation and flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant Tumours (SMQ) Narrow Subcategory-Skin malignant tumours (SMQ) Narrow
Tumor lysis syndrome	Tumor lysis syndrome (SMQ) Narrow
Infections	Infections and Infestations SOC
Opportunistic infections	Subcategory- Opportunistic infections (CMQ)
Anemia	Anaemia PT, Hemoglobin decreased PT
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anaemia PT, Hemoglobin decreased PT

Abbreviations: AESI, adverse event of special interest; CMQ, Customized MedDRA Query; PT, Preferred Term; SMQ, Standardized MedDRA Query; SOC, System Organ Class.

Incidence of all AESIs, AESIs with grade 3 or above, serious AESIs, AESIs leading to treatment discontinuation, AESIs leading to dose modification (dose interruption or dose reduction), AESIs leading to death, and treatment-related AESIs will be summarized by AESI category and PT. AESI will also be summarized by category, PT, and maximum severity.

Exposure-Adjusted Incidence Rates (EAIR)

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

The incidence rate for a patient is derived from the duration of treatment exposure of that patient. A patient's duration of exposure is given either 1) by the time from the first dose date to the first

event date (or exposure time if the first event has occurred after last dose date) (non-censored data), or 2) by the total duration of exposure in case the patient does not experience the event (censored data).

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

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

Whereby $TEAE_{event,i}$ represents if patient i experienced the event (1) or not (0), and $t_{event,i}$ as the time from the first dose date to the first event date (or exposure time if the first event has occurred after last dose date) (non-censored data) or total duration of treatment exposure if no event occurs (censored data).

The EAIR analysis will also be provided for serious TEAEs or TEAEs with grade 3 or above if needed.

The overall summary for TEAEs may be repeated in the first 6 month after first dose to provide temporal incidence trend. Summaries will also be provided for patients experiencing the first AESI within each exposure interval (≤ 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, and >12 months).

Subject data listings of all AEs, SAEs, treatment-related AEs, grade 3 or above AEs, AEs that led to death, AEs that led to dose modification (reduction/interruption) and AEs that led to treatment discontinuation will be provided.

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

6.5.3 Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 3.

Descriptive summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (e.g. calcium, glucose, potassium, sodium) will be summarized separately. Number (percentage) of subjects with abnormal postbaseline laboratory values will be summarized by visit and by any post-baseline visit.

Table 3 Selected Laboratory Tests

Serum Chemistry	Haematology	Urinalysis
Albumin	Hemoglobin	Urine pH
Alkaline phosphatase (ALP)	Platelet counts	Urine Specific Gravity
Alanine aminotransferase (ALT)	White blood cell (WBC) count	Urine Glucose
Aspartate aminotransferase (AST)	Neutrophil (Absolute)	Urine Protein
Calcium	Lymphocyte(Absolute)	Urine Occult Blood
Creatinine		
Glucose (Fasting)		
Lactate dehydrogenase (LDH)		
Potassium		
Sodium		
Total bilirubin (TBL)		
Uric acid		

A summary of the liver function test abnormalities will also be presented based on Hy's law laboratory criteria defined as ALT or AST > 3xULN and TBL > 2xULN and ALP < 2xULN at any post-baseline visit, where TBL and ALP were both within 28 days after ALT or AST elevation.

Subject data listings of selected hematology, serum chemistry parameters including Hy's Law index, and urinalysis will be provided.

6.5.4 Vital Signs

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

6.5.5 Electrocardiograms (ECG)

ECG assessments will be performed at Screening and EOT visit. Descriptive statistics for ECG parameters (heart rate, PR, QRS, QT and QTcF interval) and change from baseline will be presented.

6.5.6 Eastern Cooperative Oncology Group (ECOG)

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized. ECOG scores will be summarized by visit.

6.6 OTHER ANALYSES

Additional exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

7 INTERIM ANALYSIS

Not applicable.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9 REFRENCES

1. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time[J]. Biometrics, 1982, 38(1):29-41.
2. Cheson B D, Fisher R I, Barrington S F, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[J]. Journal of Clinical Oncology, 2014, 32(27):3059-3068.
3. Food and Drug Administration. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007, https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf
4. Kalbfleisch, J. D. and Prentice, R. L. (1980), The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.
5. National Cancer Institute. Common Toxicity Criteria for Adverse Events, Version 4.03. Cancer Therapy Evaluation Program. 14 June 2010.
6. Schemper M, Smith T L. A note on quantifying follow-up in studies of failure time.[J]. Controlled Clinical Trials, 1996, 17(4):343-346.

10 APPENDIX

10.1 APPENDIX 1: MISSING DATA IMPUTATION RULE

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

10.1.1 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 partially missing, impute as follows:

- If both month and day are missing, then set to January 01 or treatment start date if they have the same year, whichever is later.
- If only day is missing, then set to the first day of the month or treatment start date if they have the same month and year, whichever is later.
- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

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

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

If the imputed adverse event end date > death date or end of study date, then set to the death date or end of study date, whichever occurs first.

10.1.2 Prior/Concomitant Medications/Procedures

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

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

If the imputed end date > death date or end of study date, then set to the death date or end of study date, whichever occurs first.

10.1.3 Initial Diagnosis and Most Recent Progression Relapse

If the initial diagnosis date 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 day of the month

If most recent progression relapse date 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 day of the month

If the initial diagnosis date or most recent progression relapse date is completely missing, do not impute. If the imputed initial diagnosis date or most recent progression relapse date is on or after the treatment start date, then set to treatment start date-1.

10.2 APPENDIX 2 REVISED CRITERIA FOR RESPONSE ASSESSMENT OF LYMPHOMA (CHESON ET AL)

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

Positron emission tomography-computed tomography (PET-CT) should be used for response assessment in fluorodeoxyglucose (FDG)-avid histologies (using the 5-point scale provided in the footnote of the table); computer tomography (CT) is preferred for low or variable FDG avidity.

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

Response and site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5-point scale [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete mediastinum response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Progressive disease	Progressive metabolic response	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1,5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions> 2 cm In the setting of splenomegaly[c], the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If not prior splenomegaly, must increase by at least 2 cm from baseline
		New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transvers diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs). GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow). FDG uptake may be greater than

the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5-point scale:
1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

c Splenomegaly = vertical spleen length > 13 cm (reference: Cheson, BD et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014; 32:3059–3068).

10.3 APPENDIX 3 SAFETY MONITORING COMMITTEE CHARTER