BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-113
Study Protocol Title:	A Drug–Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-Cell Malignancies
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
BID	twice a day
BMI	body mass index
BTK	Bruton tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic lymphoma
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450, family 3, subfamily A
DDI	drug-drug interaction
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBC	hepatitis C virus
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PK	pharmacokinetic

PR	partial response
PT	preferred term
QD	once a day
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	system organ class
TEAE	treatment-emergent adverse event
TTR	time to response
VGPR	very good partial response
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström macroglobulinemia

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) version 2.0 is to describe the procedures and statistical methods that will be used in the clinical study report (CSR) for study BGB-3111-113, titled *A Drug–Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-Cell Malignancies*. The focus of this SAP is the planned final analyses for the clinical and pharmacokinetic (PK) data. This SAP is based on amendment 2.0 (05 November 2020) of the protocol.

2 STUDY OVERVIEW

This is a multicenter, Phase 1, open-label, randomized clinical drug-drug interaction (DDI) study of zanubrutinib in approximately 30 patients with B-cell malignancies (15 in each arm) to ensure that 24 patients (12 in each arm) complete the study. The study will include a pharmacokinetic (PK) study (Arm A and Arm B) in Cycle 1, as part of a Treatment Phase of six treatment cycles. Patients who continue to derive clinical benefit from zanubrutinib in the presence of acceptable tolerability at the end of the Treatment Phase (6 cycles) will be eligible to continue to receive zanubrutinib under a rollover extension study. Patients will be randomized to Arm A (moderate CYP3A inhibitors of fluconazole and diltiazem) or Arm B (strong CYP3A inhibitors of voriconazole and clarithromycin) to assess the effects of CYP3A inhibitors on zanubrutinib's PK in Cycle 1. Efficacy will be investigated during the subsequent treatment cycles and clinical safety will be investigated throughout the study.

The study is composed of an initial Screening phase (up to 28 days), a randomized Treatment Phase of 6 cycles including PK assessments in Cycle 1, and a Safety Follow-up phase or rollover to a long-term extension study.

Figure 1 provides the schema for the study.

Figure 1 Schema for Study BGB-3111-113

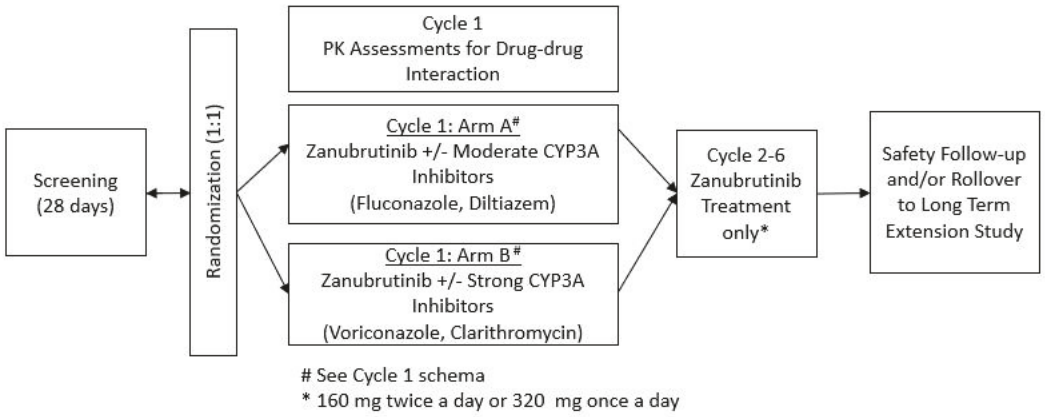
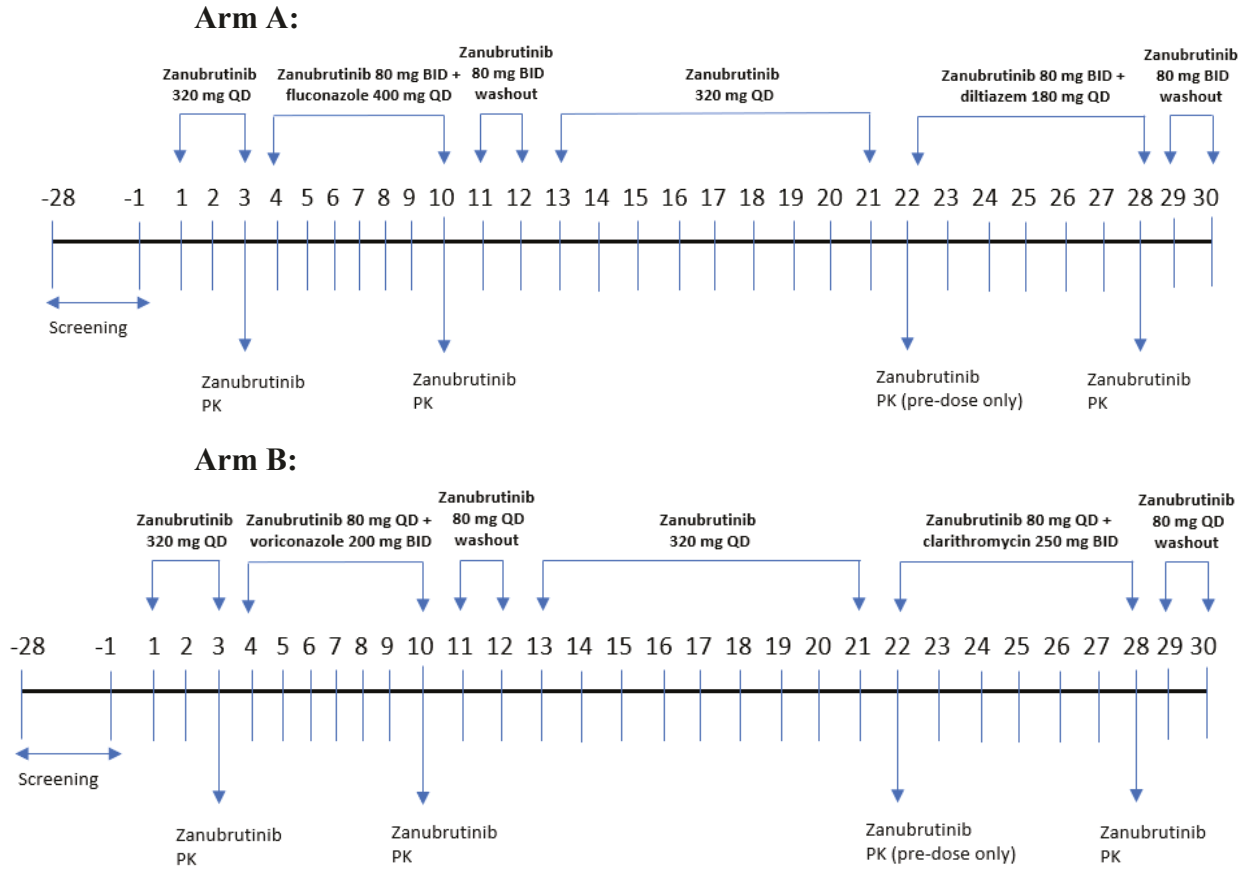


Figure 2 provides the schema for the PK assessments in Cycle 1 as described in amendment 2.0 of the protocol.

Figure 2 Schema for PK Assessments in Cycle 1 of Study BGB-3111-113



Blood samples for PK assessments will be collected during Cycle 1 on Days 3, 10, and 28 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 10 hours post-dose and on Day 22 at pre-dose. Under the original protocol, there was no pre-dose sample collected on Day 22 and the sample collection on Day 28 was prescribed to be done on Day 26. One patient was enrolled under the original protocol.

For Cycles 2-6, patients in both arms receive zanubrutinib at a dose of 160 mg (80 mg x 2 capsules) BID or 320 mg (80 mg x 4 capsules) QD. Zanubrutinib continues until progressive disease (PD), unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or end of study participation (completion of 6 cycles), whichever occurs first.

Response will be based on the investigator's assessment at the end of Cycles 3 and 6 using standard response criteria for each histologic subtype, as described in the protocol. For patients with mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), or small lymphocyte lymphoma (SLL), response will be assessed and categorized per Lugano Classification for non-Hodgkin lymphoma (NHL). For patients with chronic lymphocytic lymphoma (CLL), disease response will be determined in accordance with the 2018 International Workshop on Chronic Lymphocytic Leukemia guidelines with modification for treatment-related lymphocytosis. Response will be evaluated for the Waldenström macroglobulinemia (WM) patients using an adaptation of the consensus panel criteria updated at the Sixth International Workshop. The response categories are complete response (CR), very good partial response (VGPR, for WM),

partial response (PR), minor response (MR, for WM), stable disease, and PD. For patients with WM, quantitative immunoglobulins and β2-microglobulin will be measured on Day 1 of each cycle. Other efficacy measures are described in the protocol.

All adverse events (AEs) and serious adverse events (SAEs), regardless of relationship to zanubrutinib, will be reported until 30 days after the last dose of zanubrutinib. After this period, the investigator should report any SAEs that are believed to be related to prior zanubrutinib treatment.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objective of the study is to assess the DDI between zanubrutinib and moderate (diltiazem, fluconazole) and strong (clarithromycin, voriconazole) CYP3A inhibitors in patients with B-cell malignancies as measured by the steady-state zanubrutinib PK when coadministered with moderate and strong CYP3A inhibitors.

3.2 SECONDARY OBJECTIVES

The secondary objective is to evaluate the safety and tolerability of zanubrutinib alone and when co-administered with moderate and strong CYP3A inhibitors.

3.3 EXPLORATORY OBJECTIVES

The exploratory objective is to evaluate the efficacy of zanubrutinib.

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

The primary endpoints are the PK parameters of area under the plasma concentration-time curve from zero to the last measurable concentration (AUC_{0-t}), AUC from 0 to 24 hours (AUC_{0-24h}), maximum observed plasma concentration (C_{max}), time to reach the C_{max} (T_{max}), and apparent terminal elimination half-life ($t_{1/2}$) as determined by blood samples collection during Cycle 1 on Day 3, Day 10, and Day 28.

4.2 SECONDARY ENDPOINTS

The secondary endpoints are safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Safety will be measured by the incidence, timing, and severity of treatment-emergent AEs (TEAEs, defined in Section 6.2.1) according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

4.3 EXPLORATORY ENDPOINTS

The exploratory endpoints are:

- Overall response rate (ORR), defined as the proportion of patients who achieve a PR or better for MCL and MZL patients, and PR with lymphocytosis or better for CLL/SLL patients. For WM patients, ORR is defined as the proportion of patients achieving CR, VGPR, PR or MR.
- Rate of CR or complete metabolic response, defined as the proportion of patients who achieve a CR or complete metabolic response.
- Time to response, defined as time from randomization to the first documentation of response.

5 SAMPLE SIZE CONSIDERATIONS

Up to 30 patients will be enrolled in the study to ensure that 12 patients per arm successfully complete Cycle 1. The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

The Safety analysis set includes all patients who are enrolled and receive any dose of zanubrutinib. This will be the population of interest for the safety and efficacy analyses.

The PK Evaluable analysis set will include all patients who received at least 1 dose of zanubrutinib and have evaluable PK data (at least 1 PK parameter can be calculated). A patient may be excluded from the PK summary statistics and statistical analysis if the patient has an AE of vomiting that occurs at or before 2 times the median T_{max} of zanubrutinib.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Enrolled patient: a patient who was approved by the medical monitor or designee and who was enrolled by study center personnel in the Interactive Response Technology (IRT) system.

Study drug: the study drug in this study is zanubrutinib.

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). Study day 1 is defined as the date of first dose of study drug. There is no study day 0.

Treatment follow-up time: The treatment follow-up time (weeks) will be calculated as (date of the last dose of study drug – date of first dose of study drug + 1). For patients on treatment at the time of the data cutoff date, the date of the data cutoff will be used.

Study follow-up time: The study follow-up time (months) will be calculated as (date of end of study [or death] – date of first dose of study drug + 1). For patients on study at the time of the data cutoff date, the date of the data cutoff will be used.

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

Unscheduled Visits: Unscheduled measurements will not be included in by-visit table summaries and graphs but will contribute to best/worst case value where required (e.g., shift table). Listings will include scheduled, unscheduled data.

Treatment-emergent adverse event (TEAE): An AE that has an onset date on or after the date of the first dose of study drug and up to 30 days following study drug discontinuation, or the start of new anticancer therapy, whichever comes first. Worsening of a treatment-emergent AE to Grade 5 beyond 30 days after last dose of study drug is also considered a treatment-emergent AE, if it is prior to new anticancer therapy start.

Overall response rate (ORR): For WM, ORR is defined as the proportion of patients achieving a CR, VGPR, PR, or MR. ORR is defined as the proportion of patients who achieve a PR or better for MCL and MZL patients, and PR with lymphocytosis or better for CLL/SLL patients.

Rate of VGPR or better: For WM, rate of VGPR or better is defined as the proportion of patients achieving a CR or VGPR.

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

Listings will be provided for all data captured in the EDC as well as derived efficacy and pharmacokinetic variables.

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 PK, efficacy, or safety data will not be imputed unless otherwise specified.
- Time-to-event or duration of event endpoints will be based on the actual date the assessments to document response were obtained (e.g., date of IgM assessment) rather than the associated visit date.
- 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, minimum, and maximum. The first and third quartiles (Q1, Q3) may also be provided as appropriate.
- Notations in the EDC documenting assessments that were delayed or not performed due to Covid-19 will be noted in the listings. No summary of these assessments will be provided.

- If an investigator states that an adverse event is due to Covid-19, it will be documented in the verbatim term. No summary of specific Covid-19 related adverse events will be provided.

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 prior/concomitant medications/procedures, subsequent antineoplastic therapies, adverse events and deaths. Specific rules for handling of missing or partially missing dates for prior/concomitant medications/procedures, subsequent antineoplastic therapies, adverse events, and deaths are provided in Appendix A.

By-visit summaries of variables with missing data will use only non-missing data, not imputed one, unless otherwise specified.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

Not applicable.

6.2.6 Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the eCRF data and all derived values will be reviewed to ensure that the data are accurate and complete up to a pre-specified cutoff date. Consistency checks and appropriate source data verification will be completed.

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The summary of patient disposition will be based on the Safety Analysis set. The following patient disposition information will be summarized:

- Number of enrolled patients
- Number of treated patients
- Number (%) of treated patients who remain on treatment at time of data cutoff date or completion of Cycle 6
- Number (%) of treated patients who discontinued treatment prior to data cutoff date or completion of Cycle 6
- Reasons that patients discontinued treatment
- Number (%) of treated patients who remain on study at time of data cutoff date
- Number (%) of treated patients who discontinued study
- Reasons that patients discontinued study

- Treatment follow-up time (weeks)
- Study follow-up time (months)

6.3.2 Protocol Deviations

Criteria for important protocol deviations will be established, and patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized for all patients in the Safety Analysis set.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for patients in the Safety Analysis set as follows:

- Age (years) and age (years) categorized as <65 and ≥65
- Sex
- Race
- Ethnicity
- Baseline ECOG performance status
- Baseline weight (kg)
- Baseline height (cm)
- Body mass index (kg/m^2)
- Baseline viral hepatitis B and C serologic markers, including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR), hepatitis C virus (HCV) antibody, and HCV RNA by PCR.

6.3.4 Disease History and Characteristics

Disease history and disease characteristic will be summarized for the Safety Analysis set. These include:

- Disease type and sub-type, including blastic variant form of MCL
- Time since first diagnosis to Day 1 (months)
- Stage (Rai) for CLL at screening
- Stage (Binet) for CLL at screening
- Stage for NHL at screening
- Risk group for WM at screening

6.3.5 Prior Antineoplastic Therapies

The following information related to prior antineoplastic therapy will be summarized for the Safety Analysis set:

- Number of prior systemic therapy regimens and number of prior regimens categorized as 1, 2, 3, etc.
- Time from the end of last regimen to Day 1 (months)
- Reason last regimen ended
- Best overall response to last regimen
- Number (%) of patients with prior radiotherapy

6.3.6 Prior and Concomitant Medications

Concomitant medications will be assigned a preferred name using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification.

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Appendix A will be used.

The number (percentage) of patients reporting concomitant medications will be summarized by ATC medication class and WHO DD preferred name for the Safety Analysis set.

6.3.7 Medical History

Medical history will be mapped to a preferred term (PT) and a system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) of the version currently in effect at BeiGene at the time of the data cutoff date. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by SOC and PT for the Safety Analysis set.

6.4 EFFICACY ANALYSIS

The population of primary interest for efficacy analyses is the Safety Analysis set.

6.4.1 Best Response, ORR, and Rate of VGPR or Better

The ORR, rate of CR or complete metabolic response, and rate of VGPR or better (for WM) will be summarized. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders for these summaries. Best response (CR, VGPR, PR, MR, SD, PD, not evaluated) will be summarized.

6.4.2 Time to Response

Time to response (TTR) is defined as the time (weeks) from date of first dose of zanubrutinib to the earliest qualifying response of MR or better for WM, to first earliest qualifying response of PR with lymphocytosis or better for CLL, and to first earliest qualifying response of PR or better for other diagnoses. TTR will be summarized by descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) for responders only.

6.4.3 Subgroup Analyses

The summaries of ORR will be provided by diagnosis (type and sub-type of disease).

6.5 SAFETY ANALYSES

All safety analyses will be performed based on the Safety Analysis set. Safety and tolerability will be assessed, where applicable, by incidence, severity, change from baseline values, and abnormal values for all relevant parameters including AEs, laboratory parameters, vital signs, and physical examination.

6.5.1 Extent of Exposure

The following variables describing extent of exposure to zanubrutinib will be summarized descriptively:

- Number of treatment cycles received, defined as the total number and percentage of treatment cycles in which at least one dose of zanubrutinib is administered
- Duration of exposure (weeks), defined as the duration (weeks) from the date of the first dose to the last dose of zanubrutinib
- Cumulative total dose received per patient (mg), defined as the cumulative dose (mg) of zanubrutinib during the treatment period of the study
- Actual dose intensity (mg/day), defined as the total dose of zanubrutinib (mg) received by a patient divided by the duration of exposure (days)
- Relative dose intensity (%), defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (320 mg/day).

The number (percentage) of patients with dose reduction and drug discontinuation will be summarized with the respective reasons. The number of dose reductions/missed doses will be summarized.

Patients who do not receive all the CYP3A inhibitor drug doses as prescribed in the protocol will be noted as protocol deviations.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v5.0. Verbatim description of AEs (as recorded by the investigator on the eCRF) will be classified into standardized PT and SOC using MedDRA.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

Treatment-related AEs include those events considered by the investigator to be possibly or probably related to zanubrutinib or with missing assessment of the causal relationship.

An overview table, including the number (and percentage) of patients with at least one TEAE, grade 3 or above TEAE, treatment-emergent SAE, treatment-related TEAE, treatment-related grade 3 or above TEAE, treatment-related SAE, TEAE and treatment-related TEAE that led to death, TEAE and treatment-related TEAE that led to treatment discontinuation, TEAE and treatment-related TEAE that led to dose reduction, and TEAE and treatment-related TEAE that led to a missed dose will be provided.

The incidence of TEAEs will be also reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade according to CTCAE v5.0 within a SOC and PT, even if the patient experiences more than 1 TEAEs within a specific SOC and PT.

The number (percentage) of patients with at least one TEAE, grade 3 or above TEAE, treatment-emergent SAE, treatment-related TEAE, treatment-related grade 3 or above TEAE, treatment-related SAE, TEAE that led to death, TEAE that led to treatment discontinuation, and TEAE that led to dose modification will be summarized by SOC and PT. All TEAEs, grade 3 and above TEAEs, and SAEs will also be summarized by PT in descending order. All TEAEs, related TEAEs, TEAEs that led to treatment discontinuation, and TEAEs that led to a dose modification will be summarized by SOC, PT, and highest severity grade.

The incidence of TEAEs of interest, grade 3 or higher TEAEs of interest, treatment-related TEAEs of interest, and treatment-related grade 3 or higher TEAEs of interest will be summarized by category and PT.

The incidence of TEAEs with onset during Cycle 1 will be summarized by SOC and PT. This summary will be provided for each arm and treatment combination at day of onset. The groups for this summary are:

- Arm A zanubrutinib (onset of AE prior to date of first dose of fluconazole [nominally Day 4] or after discontinuation of fluconazole and prior to date of first dose of diltiazem [nominally Days 13-19])
    - zanubrutinib+fluconazole (onset of AE on or after the date of first dose of fluconazole and prior to 3 days after date of last dose of fluconazole [nominally Days 4-14])
    - zanubrutinib+diltiazem (onset of AE on or after date of first dose of diltiazem [nominally Day 22] to the end of Cycle 1)
- Arm B zanubrutinib (onset of AE prior to date of first dose of voriconazole [nominally Day 4] or after discontinuation of voriconazole and prior to date of first dose of clarithromycin [nominally Day 13-19])

- zanubrutinib+voriconazole (onset of AE on or after the date of first dose of voriconazole and prior to 3 days after date of last dose of voriconazole [nominally Day 4-14])
- zanubrutinib+clarithromycin (onset of AE on or after date of first dose of clarithromycin [nominally Day 22] to the end of Cycle 1)

Under the original protocol, diltiazem or clarithromycin dosing was to begin on Day 20 rather than Day 22. If the start of the CYP3A inhibitor differs from the prescribed start day, then the actual day will be used to define the groups for this summary.

A summary of the number of deaths and the causes of death, classified by deaths within 30 days of last dose of zanubrutinib and deaths more than 30 days after the last dose, will be provided. Cause of death will also be summarized.

Listings of deaths/fatal AEs, serious AEs, AEs leading to dose modification or discontinuation of zanubrutinib will be provided.

6.5.3 Laboratory Values

Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for hematology and serum chemistry laboratory parameters at each visit and their changes from baseline will be provided. Baseline values of coagulation parameters will be summarized.

Laboratory parameters that are graded according to CTCAE v5.0 will be summarized by CTCAE grade. Shift tables will be used to assess the shift of each laboratory parameter from its toxicity grade at baseline to the worst post-baseline toxicity grade. Parameters with CTCAE grading in both high and low directions (e.g., calcium, glucose, magnesium, phosphorus, potassium, sodium) will be summarized separately. A listing of all grade 3 or higher laboratory values will be provided.

6.5.4 Vital Signs

Values of vital signs parameters, including resting diastolic and systolic BP, heart rate, temperature, and weight, and changes from baseline will be summarized by visit and assessment time.

6.5.5 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed locally in triplicate at screening, at protocol-specified visits and timepoints during Cycle 1for all patients and as clinically indicated at other timepoints. The values and change from baseline of ECG parameters will be summarized by visit and assessment time.

6.5.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status will be summarized as the number (percentage) of patients with each ECOG grade at the screening visit, each visit during study treatment, and at the Safety follow-up

visit. Shift tables assessing the ECOG performance status at baseline versus worst performance status on study will be presented.

6.5.7 Blood Transfusions

The number (percentage) of patients reporting one or more blood transfusions will be summarized by type of product for the Safety Analysis set.

6.6 PHARMACOKINETIC ANALYSES

The following PK parameters will be determined where possible from the plasma concentrations of zanubrutinib using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{0-t}	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (T_{last})[b]
AUC_{0-24h}	h*ng/mL	area under the concentration-time curve from time 0 extrapolated to 24 hours
C_{max}	ng/mL	maximum observed concentration
T_{max}	H	time of the maximum observed concentration
$t_{1/2}$	H	apparent terminal elimination half-life

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

The following additional PK parameters may be determined where appropriate.

Parameter	Units[a]	Definition
$\%AUC_{extrap}$	%	percentage of AUC due to extrapolation from the last quantifiable concentration to infinity
T_{last}	H	time of the last quantifiable concentration
CL/F	L/h	apparent oral clearance
AUC_{0-12h}	h*ng/mL	area under the concentration-time curve from time 0 extrapolated to 12 hours
V_z/F	L	apparent volume of distribution

Pharmacokinetic analysis will be carried out where possible using actual blood sampling times post dose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

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}.

For the calculation of AUC_{0-12h}, AUC will be extrapolated to 12 hours for both the QD and BID dose regimens and for the calculation of AUC_{0-24} , AUC will be extrapolated to 24 hours post dose for the QD dose; and for the BID dose regimen, the AUC_{0-24} will be estimated as twice that of AUC_{0-12h}. The specific algorithm for the estimation will be documented in the study report.

6.6.1 Calculation of Pharmacokinetic Parameters

6.6.1.1 Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each patient will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥ 0.7.

Parameters requiring λ_z for their calculation (eg, AUC_{0-24h}, $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2-adj value of the regression line is ≥ 0.7.

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥ 2 half-lives. If the λ_z Span Ratio is < 2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

6.6.1.2 Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of area under the concentration-time curve (AUC) will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

If the extrapolated area is > 30%, $AUC_{0\text{-}24h}$ (and derived parameters) may be excluded from the summary statistics and statistical analysis at the discretion of the pharmacokineticist.

If $AUC_{0\text{-}24h}$ cannot be determined reliably for all patients and/or treatments, an alternative AUC measure, such as AUC to a fixed time point or $AUC_{0\text{-}t}$, may be used in the statistical analysis.

6.6.1.3 Criteria for Handling Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQs will be treated as missing. The following rules apply with special situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.

6.6.2 Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

6.6.3 Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ± 10%, the concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will apply for the summaries and figures:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% of geometric mean will be reported as not calculated (NC).

All PK concentrations and parameters, with the exception of diagnostic regression-related PK parameters, will be summarized. The summary tables will include n, arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum. For the concentration data and all PK parameters except T_{max} and T_{last}, the geometric mean and geometric coefficient of variation (GCV) will be provided. The GCV is calculated as $GCV(\%) = [\exp(s^2) - 1]^{½} \times 100$ where s^2 is the sample variance of the ln transformed data.

The following figures will be provided:

- Mean (+ standard deviation [SD]) PK concentration versus time post dose for each PK visit. The values for each PK visit will be displayed on the same set of axes within each arm of the study.
- Individual concentration data versus time post dose for each PK collection visit day will be provided. The values for each PK visit will be displayed on the same set of axes within each arm of the study.
- Mean (+ SD) of the PK parameters for each PK visit within each arm of the study.
- Individual values of the PK parameters for each PK visit within each arm of the study

All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will only be displayed on the linear scale.

6.6.4 Statistical Methodology for Analysis of Pharmacokinetic Parameters

Four separate statistical analyses will be conducted in order to investigate the DDI of the 4 CYP3A inhibitors on the PK of zanubrutinib as evaluated by zanubrutinib C_{max}, AUC_{0-t}, and $AUC_{0–24h}$. The values on Day 3 in the absence of CYP3A inhibitors will be compared to the values on Day 10 and Day 28 in the presence of CYP3A inhibitors. These analyses will be performed separately for each treatment arm. Additional PK parameters may be analyzed as needed.

PK analysis 1: Arm A only	Compare Day 3 (zanubrutinib alone) to Day 10 (zanubrutinib + fluconazole)
PK analysis 2: Arm A only	Compare Day 3 (zanubrutinib alone) to Day 28 (zanubrutinib + diltiazem)
PK analysis 3: Arm B only	Compare Day 3 (zanubrutinib alone) to Day 10 (zanubrutinib + voriconazole)
PK analysis 4: Arm B only	Compare Day 3 (zanubrutinib alone) to Day 28 (zanubrutinib + clarithromycin)

The natural log (ln)transformed PK parameters will be analyzed using a mixed model. The model will include treatment as a fixed effect, and patient as a random effect. Each analysis (PK analysis 1-4) will be conducted separately in a model with relevant data of test and difference (e.g., Parameters from Day 28 will not be included in the statistical model of PK analysis 1).

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% confidence interval (CI) will be calculated; these values will then be back-transformed to give the geometric least square mean (GLSM), ratio of GLSMs for zanubrutinib + CYP3A inhibitor to zanubrutinib alone and corresponding 90% CI.

Additionally, the pooled estimate (across all treatments) of the within-patient coefficient of variation (CV_W) will be calculated. The CV_W is defined as

$$CV_W(\%) = [\exp(MSE) - 1]^{1/2} \times 100$$

where MSE is the residual error from the mixed model.

An example of the SAS code that will be used is as follows:

Mixed Model Analysis

```
proc mixed data = <data_in>;
  by param;
  class trt usubjid;
  model lpk = trt / cl residual ddfm = kr2;
  lsmeans trt / cl pdiff = control('1') alpha = 0.1;
  random usubjid;
  ods output lsmeans = <data_out>;
  ods output diffs = <data_out>;
  ods output covparms = <data_out>;
run;
```

6.7 Additional Exploratory 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

No formal interim analyses are planned for this study. Data from the study will be reviewed by the study team on a periodic basis. Summaries and analyses of subsets of the study data may be performed on a periodic basis for study team review, submission to professional meetings, and internal decision-making.

8 CHANGES IN THE PLANNED ANALYSIS

The table below summarizes the changes in the planned analyses from SAP 1.0. The changes are all made before database lock.

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	25 March 2021	Protocol V2.0		

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
2.0	This version	SAP V1.0	Correct the analyses per protocol amendment and inconsistencies with eCRF. Provide more details of PK analyses.	The PK assessment and relevant analyses on Day 26 are changed to Day 28. The calculation of AUC_{0-12h} and AUC_{0-24h} are further detailed. The residual plot for model diagnosis is removed. The summary of reasons for missed doses, prior stage/prognostic factors for WM patients, and prior transplants are removed.

9 REFERENCES

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10 APPENDIX

Appendix A: 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.

A.1 Prior/Concomitant Medications/Therapies/Procedures

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

If start date of a medication/therapy/procedure/transfusion 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/transfusion 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
- For prior anticancer therapy, the imputed end date should be the first dose date – 14 at the latest after imputation.

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

A.2 Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

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

- If both month and day are missing and year = year of treatment start date, then set to treatment start date

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

If end date of an AE 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 AE end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

A.3 Deaths

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

A.4 Subsequent Antineoplastic Therapies

If the start date of a subsequent antineoplastic therapy is missing, the start date will be assumed to be on the 1st date of the month. If the imputed start date ≤ end of treatment date, then set to 1 day after the last treatment date.

Appendix B: Sensitivity Analysis for PK Parameters

A second method for the statistical analysis of the PK parameters will be performed in order to adjust the effect of each CYP3A inhibitor on the pharmacokinetics of the other CYP3A inhibitor each patient receives. Two separate statistical analyses will be conducted, one for each treatment arm. The values on Day 3 in the absence of CYP3A inhibitors will be compared to the values on Day 10 and Day 28 in the presence of CYP3A inhibitors.

PK analysis 1: Arm A only	Compare Day 3 (zanubrutinib alone) to Day 10 (zanubrutinib + fluconazole) and Day 28 (zanubrutinib + diltiazem)
PK analysis 2: Arm B only	Compare Day 3 (zanubrutinib alone) to Day 10 (zanubrutinib + voriconazole) and Day 28 (zanubrutinib + clarithromycin)

The SAS code will be essentially the same as for the primary comparisons. The covariance structure will be set to UN for the mixed model analyses. However, two separate contrasts will be provided for the difference in the least squares means for comparison of zanubrutinib to zanubrutinib + each CYP3A inhibitor.