Summary of Amended Protocol Changes

A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects

Protocol Amendment 1 Status: Final
Original Protocol (Version 1) Date: 15 June 2020
Protocol Version 2 Date: 16 July 2020

Investigational Product: Zanubrutinib (BGB-3111)

Protocol Reference Number: BGB-3111-112
Covance Study Number: 8426473
IND Number: 125326

Sponsor:
BeiGene, Ltd.
c/o BeiGene USA, Inc.
2955 Campus Drive, Suite 200
San Mateo, California 94403
USA

Study Site:
Covance Clinical Research Unit Inc.
1900 Mason Avenue, Suite 140
Daytona Beach, Florida 32117
USA

Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

NCT04470908

The primary changes in this amendment are:

1. Reference to pharmacogenetics blood sampling was removed from Appendix 3 Total Blood Volume and Appendix 5 Schedule of Assessments, as this is not required for this study.

Minor changes:

1. Appendix 5 Schedule of Assessment footnote designations were updated to account for removal of footnote “d”, which was previously associated with pharmacogenetics blood sampling.
2. Appendix 3 Total Blood Volume total was reduced by 5 mL due to removal of pharmacogenetics blood sampling from the table.
3. The amendment/version number and date were updated throughout the protocol.

Protocol

A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects

Protocol Status: Final
Protocol Date: 16 July 2020
Protocol Version: 2

Investigational Medicinal Product: Zanubrutinib (BGB-3111)

Protocol Reference Number: BGB-3111-112
Covance Study Number: 8426473
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San Mateo, California 94403
USA

Study Site:
Covance Clinical Research Unit, Inc.
1900 Mason Ave. Suite 140
Daytona Beach, Florida 32117
USA

Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol "A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects" and approve it:

[redacted]

17-Jul-2020 | 11:37:37 PDT

Date

BeiGene, Ltd.

INVESTIGATOR AGREEMENT

I have read the protocol "A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects" and agree to conduct the study as described herein and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained in this protocol will be published or disclosed without prior WRITTEN approval from sponsor.

[redacted]

20 JUL 2020
Date

STUDY IDENTIFICATION

Sponsor	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
Sponsor's Study Contact	[redacted] 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA Tel: [redacted]
Sponsor's Medical Contact	[redacted] 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA Tel: [redacted]
Study Site	Covance Clinical Research Unit, Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117 USA
Principal Investigator	[redacted] Covance Clinical Research Unit, Inc. 1900 Mason Avenue, Suite 140 Daytona Beach, FL 32117 USA Tel: [redacted]
Sub-investigator(s)	Obtain information from Form FDA 1572
Clinical Laboratory	LabCorp 4200 North 29 Avenue Hollywood, FL 33020 USA
Bioanalytical Laboratory	XenoBiotic Laboratories, Inc. 107 Morgan Lane Plainsboro, NJ 08536 USA
Statistician	[redacted] Covance

SYNOPSIS

Title of study: A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects

Objectives:

The primary objective of the study is:

- to determine the effect of the moderate cytochrome P450 (CYP)3A inducer, rifabutin, on the pharmacokinetics (PK) of zanubrutinib in healthy male subjects.

The secondary objective of the study is:

- to evaluate the safety and tolerability of zanubrutinib when coadministered with rifabutin in healthy male subjects.

Study design:

This will be an open-label, fixed-sequence study in healthy male subjects to investigate the effect of CYP3A induction by steady-state rifabutin on the single dose PK of zanubrutinib.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1.

A single-dose administration of zanubrutinib on Day 1 will be followed by a 36-hour PK sample collection period for analysis of zanubrutinib. Subsequently, following rifabutin administration on Days 3 to 10, a single dose of zanubrutinib will be coadministered with rifabutin on Day 11 followed by a 36-hour PK sample collection period for analysis of zanubrutinib. Subjects will be confined to the CRU until discharge on Day 13. A follow-up visit will be scheduled on Day 19 (± 1 day).

Number of subjects:

Approximately 15 subjects will be enrolled to ensure that 12 subjects complete the study.

Diagnosis and main criteria for inclusion:

Healthy male subjects aged between 18 and 65 years, inclusive, at screening; with a body mass index between 18.0 and 32.0 kg/m^2, inclusive, at screening.

Test products, dose, and mode of administration:

- Single dose of 320 mg zanubrutinib, given orally as 4 × 80-mg capsules in the fasted state, on Days 1 and 11
- 300 mg rifabutin once daily, given orally as 2 × 150-mg capsules with food on Days 3 to 10 and fasted on Day 11

Duration of treatment:

Planned screening duration: approximately 4 weeks

Length of clinic confinement: Days -1 to 13

Outpatient follow-up visit: 6 days (± 1 day) after clinic discharge

Planned study duration (screening to follow-up): approximately 7 weeks

Criteria for evaluation:

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of zanubrutinib at the following timepoints (relative to zanubrutinib dosing): predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours postdose. The PK parameters of zanubrutinib following zanubrutinib dosing on Days 1 and 11 will be calculated using standard noncompartmental methods. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), time of the maximum observed concentration (T_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F). Other PK parameters may be reported.

Safety:

Safety endpoints for this study include adverse events (AEs), clinical laboratory evaluations, vital sign assessments, 12-lead electrocardiograms (ECGs), and physical examinations.

Statistical methods:

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.

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

The Safety Population will include all subjects who received at least 1 dose of zanubrutinib.

The primary PK parameters are AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, and V_z/F for zanubrutinib following zanubrutinib dosing on Days 1 and 11. Other PK parameters may be reported but will be regarded as secondary and will not be subject to inferential statistical analysis. A linear mixed-model analysis will be applied to analyze the log-transformed primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}). The model assumes a fixed effect for treatment and a random effect for subject. Estimates of geometric mean ratios together with the corresponding 90% confidence intervals will be derived for the comparisons of the PK parameters as follows:

- zanubrutinib plus rifabutin (test) versus zanubrutinib alone (reference)

All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and by association with the study drugs, as determined by the investigator. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory evaluations data, 12-lead ECGs, and vital signs will be listed and summarized descriptively. Clinical laboratory data with values outside of the normal ranges will be identified. Observed values and changes from baseline laboratory data, vital signs, and ECG results will be summarized by visit.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
CRO	contract research organization
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SOP	standard operating procedures
$t_{1/2}$	apparent terminal elimination half-life
T_{max}	time of the maximum observed concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution

1. INTRODUCTION

Refer to the Zanubrutinib Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of zanubrutinib.

1.1. Overview

Bruton's tyrosine kinase (BTK) is a signaling molecule that is predominantly expressed in B-lymphocytes at various stages of development. Activation of BTK in B-cells initiates a series of signaling events, including recruitment of BTK to the plasma membrane, autophosphorylation at tyrosine 223, activation of phospholipase Cγ2, subsequent nuclear factor κB activation, and expression of genes involved in proliferation and survival.[2,3,4] Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Zanubrutinib (BRUKINSA™; also known as BGB-3111), a BTK inhibitor, has been granted an accelerated approval by the US Food and Drug Administration (FDA) on 14 November 2019 for the indication of treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.

Zanubrutinib is a novel, second-generation, small molecule oral inhibitor of BTK that works by forming an irreversible covalent bond at Cys481 within the adenosine triphosphate binding pocket of BTK. Zanubrutinib has been shown to be more selective than ibrutinib, an approved agent, for inhibition of BTK against off-target kinases, including EGFR, JAK3, HER2, TEC, inducible tyrosine kinase, and others based on results from kinase inhibition and cell-based assays. The increased selectivity of zanubrutinib for BTK may result in a lower incidence and severity of off-target toxicities linked to inhibition of the aforementioned kinases. Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab induced, antibody-dependent cell-mediated cytotoxicity, consistent with its more selective activity against BTK and weaker inducible tyrosine kinase inhibitory activity than ibrutinib, as revealed in both biochemical and cellular assays.

Zanubrutinib is being developed by BeiGene, Ltd. as a second-generation inhibitor of BTK for the treatment of B-cell malignancies, including mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström's macroglobulinemia, follicular lymphoma, marginal zone lymphoma, and diffuse large B-cell lymphoma, as a monotherapy and/or in combination with other agents. Zanubrutinib entered global clinical development in August 2014 and is being investigated in ongoing Phase 1, 2, and 3 studies in patients with B-cell malignancies.[1]

1.2. Summary of Clinical Experience

As of 31 August 2019, 15 clinical studies investigating zanubrutinib in patients are ongoing, with preliminary results summarized in the IB.[1]

Additionally, a total of 6 Phase 1 clinical pharmacology studies have been conducted and completed.

1.2.1. Summary of Safety in Humans

Single doses of 320 mg zanubrutinib, as detailed in Table 1, were safe and well tolerated in healthy subjects. The results of these studies and other completed Phase 1 studies at other dose levels of zanubrutinib are summarized in the IB.[1]

Table 1: Summary of Safety in Healthy Subjects Receiving Single Oral Doses of 320 mg Zanubrutinib

Study	Outcome	Summary of Safety
BGB-3111-103, Phase 1 food effect study	No unexpected safety issues identified. Oral doses of 320 mg zanubrutinib were safe and well tolerated in healthy subjects.	Overall, 40 TEAEs were reported for 14 (77.8%) of 18 subjects. Most frequently reported TEAEs (≥10% of subjects overall) were headache (4 [22.2%] subjects), lymphadenopathy (3 [16.7%] subjects), pharyngitis, catheter site pain, ECG QT prolonged, contusion, skin abrasion, and rhinorrhoea (2 [11.1%] subjects each). Fourteen drug-related TEAEs were reported for 10 (55.6%) subjects. In the fasted state, a severe TEAE (pyelonephritis) was reported for 1 (6.7%) subject. No deaths or SAEs were reported. Three (16.7%) subjects had TEAEs that led to discontinuation of study. The TEAE of ECG QT prolonged led to discontinuation in 2 subjects (both assessed by the investigator as not related to study drug), and the TEAE of pyelonephritis led to discontinuation in 1 subject (assessed by the investigator as severe in intensity and related to study drug).
BGB-3111-104, Phase 1 DDI study	Single doses of 320 mg and 20 mg zanubrutinib administered alone and coadministered with 600 mg rifampin and 200 mg itraconazole, respectively, were safe and well tolerated in healthy subjects.	None of the 38 subjects dosed in the study reported a TEAE higher than Grade 2 or an SAE, and no subject discontinued due to a TEAE. The majority of TEAEs were considered not related to the study drugs, were Grade 1 in severity, and resolved without treatment. No clinically significant changes or findings were noted in clinical laboratory evaluations, vital signs, physical examinations, or body weight in this study. No subject had a QTcF value >450 msec or an increase from baseline in QTcF of >60 msec during the study.
BGB-3111-105, Phase 1 AME study	A single oral dose of 320 mg of zanubrutinib containing ~200 µCi of [^{14}C]-zanubrutinib was well tolerated in healthy male subjects.	Overall, 13 TEAEs were reported for 4 (66.7%) of 6 subjects. All TEAEs were mild in severity. Two (33.3%) subjects reported a total of 2 TEAEs that were considered to be possibly related to study drug. All of the remaining 11 TEAEs were considered to be unlikely related or not related to study drug. The most frequently reported TEAEs by SOC were GI disorders; 4 (66.7%) subjects reported a total of 9 TEAEs in this SOC. These TEAEs were assessed as being unlikely related or not related to study drug. The next most frequently reported TEAEs by SOC were nervous system disorders; 2 (33.3%) subjects reported TEAEs of dizziness that were assessed as being possibly related to study drug. These TEAEs resolved on the same day without concomitant medication. All other TEAEs in the study were assessed as being either unlikely related to study drug or not related to study drug. All TEAEs resolved by the end of the study without intervention. There were no deaths, other SAEs, or severe TEAEs reported and no subjects withdrew from the study because of a TEAE.

Abbreviations: AME = absorption, metabolism, and excretion; DDI = drug-drug interaction; ECG = electrocardiogram; GI = gastrointestinal; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

1.2.2. Summary of Pharmacokinetics, Pharmacodynamics, and Product Metabolism in Humans

Zanubrutinib was rapidly absorbed and eliminated after oral administration in humans. The peak concentrations occurred around 2 hours postdose and the mean apparent terminal elimination half-life ($t_{1/2}$) was approximately 2 to 4 hours. The maximum observed concentration (C_{max}) and the drug exposure (the area under the concentration-time curve [AUC]) increased in a nearly dose proportional manner from 40 mg to 320 mg, both after single-dose and repeat-dose administration. A food effect study (BGB-3111-103) indicated that coadministration with food did not appear to significantly impact the pharmacokinetics (PK) of zanubrutinib.

A human absorption, metabolism, excretion study indicated that zanubrutinib was primarily eliminated by hepatic metabolism and fecal excretion. Approximately 87.1% of the radiolabeled dose was excreted in feces with only 0.4% of the dose excreted in urine as parent drug. Cytochrome P450 (CYP)3A isoenzymes are the principal metabolic pathway for zanubrutinib.

A clinical drug-drug interaction (DDI) study was conducted to assess the potential impact of CYP3A modulators on the exposure of zanubrutinib in healthy volunteers (BGB-3111-104). Results indicated that coadministration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once daily [QD]) decreased exposure of zanubrutinib in healthy volunteers by 13.5-fold for AUC from time zero to infinity ($AUC_{0-\infty}$), and 12.6-fold for C_{max}. Coadministration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg QD) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$ and by 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. Additionally, a physiologically-based PK model was developed and was used to predict the effect of CYP3A inhibitors and CYP3A inducers on the PK of zanubrutinib. Physiologically-based PK simulations suggest that coadministration of multiple doses of a moderate CYP3A inhibitor (eg, fluconazole, diltiazem, and erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. Exposure increases were less than 1.5-fold with a mild CYP3A inhibitor. Physiologically-based PK simulations suggest that a moderate CYP3A inducer (eg, efavirenz) may decrease the C_{max} and AUC of zanubrutinib by approximately 2- to 3-fold. A clinical DDI study (BGB-3111-108) showed that zanubrutinib had no effect on a CYP2C9 substrate (warfarin) and a breast cancer resistance protein substrate (rosuvastatin). Zanubrutinib is a mild CYP3A and CYP2C19 inducer.

A dedicated hepatic impairment study (BGB-3111-107) showed that there was no substantial difference in PK between patients with mild/moderate hepatic impairment and healthy subjects. The total and unbound AUC of zanubrutinib in subjects with severe hepatic impairment were 1.60- and 2.94-fold, respectively, of those in healthy controls.

1.3. Study Rationale

Given the decreased exposure of approximately 13-fold for zanubrutinib when administered with a strong CYP3A inducer (rifampin) as determined in study BGB-3111-104, a clinical DDI study is warranted to determine the extent of interaction with moderate CYP3A inducers. Among the recommended moderate CYP3A inducers for DDI evaluation, rifabutin

was selected in this study as it is more clinically relevant in the target patient population of zanubrutinib. There have been cases in zanubrutinib clinical trials where prescribing of an anti-tuberculosis agent such as rifampin or rifabutin was warranted. Rifabutin is a first-line therapeutic alternative to rifampin (ie, due to intolerance to or unacceptable drug interactions with medication coadministered with rifampin) in the treatment of drug-sensitive tuberculosis.[5] With rifampin being a potent CYP3A inducer that should be avoided during coadministration of zanubrutinib, evaluating the PK of zanubrutinib coadministered with rifabutin would be clinically meaningful. Furthermore, since HIV patients are excluded from zanubrutinib clinical trials, studies with moderate CYP3A inducers such as efavirenz and etravirine (for the treatment of HIV infection) would not be as informative. Results from this study could be used to directly impact dose adjustment recommendation in ongoing zanubrutinib studies and to support dose recommendation when zanubrutinib is coadministered with drugs that are moderate CYP3A inducers.

1.4. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with zanubrutinib may be found in the IB.[1]

More information about the known and expected benefits and risks of rifabutin may be found in the prescribing information.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to determine the effect of the moderate CYP3A inducer rifabutin on the PK of zanubrutinib in healthy male subjects.

The secondary objective of the study is:

- to evaluate the safety and tolerability of zanubrutinib when coadministered with rifabutin in healthy male subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

The PK outcome endpoints of zanubrutinib derived from the plasma concentration-time profiles following oral administration of zanubrutinib on Days 1 and 11 are as follows:

- AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t})
- $AUC_{0-\infty}$
- C_{max}
- time of the maximum observed concentration (T_{max})
- $t_{1/2}$
- apparent oral clearance (CL/F)
- apparent volume of distribution (V_z/F).

Other PK parameters may also be reported.

2.2.2. Secondary Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- vital sign measurements
- 12-lead electrocardiogram (ECG) parameters
- physical examinations.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be an open-label, fixed-sequence study in healthy male subjects to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib.

Approximately 15 subjects will be enrolled to ensure that 12 subjects complete the study.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1. All subjects will receive the following treatments:

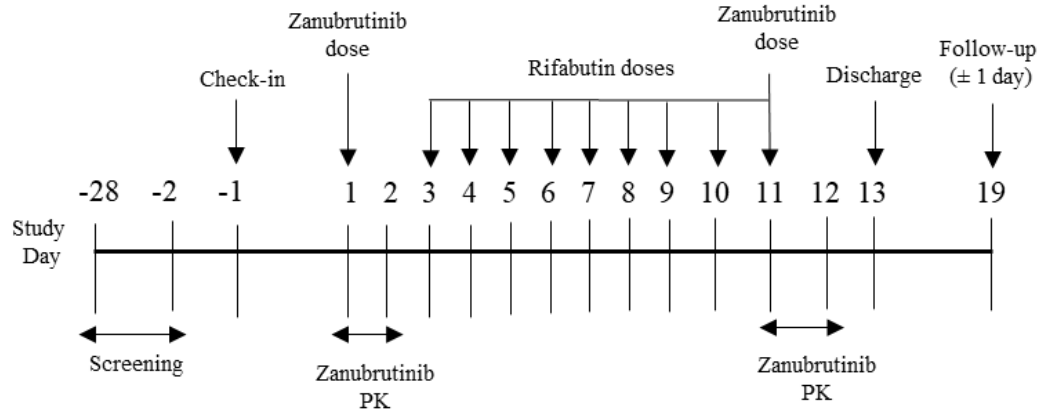
- Day 1: single oral dose of 320 mg zanubrutinib after overnight fast of 8 to 10 hours
- Days 3 to 10: oral dose of 300 mg rifabutin QD with food (standard meal)
- Day 11: single oral dose of 320 mg zanubrutinib and QD dose of 300 mg rifabutin after overnight fast of 8 to 10 hours.

On Days 1 and 11, serial blood collections will be obtained from predose through 36 hours postdose for analysis of plasma concentrations of zanubrutinib (and metabolites, if applicable). A Schedule of Assessments is presented in Appendix 5.

Subjects will be confined to the CRU until discharge on Day 13. A follow-up visit will be scheduled on Day 19 (± 1 day). A subject will be considered to have completed the study when they have participated in the follow-up visit.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



The maximum total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 7 weeks.

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 5.

3.2. Discussion of Study Design

This study is designed to evaluate the effect of rifabutin (a moderate CYP3A inducer) on the PK of zanubrutinib in healthy subjects. The fixed-sequence design used in this study is typical for interaction studies where a relatively small number of subjects are required, because it allows intrasubject comparisons and reduces intersubject variability. This study will be open-label as the study endpoints are objective rather than subjective; therefore, investigators and subjects do not need to be blinded.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Inducer Selection

Rifabutin has been used as a moderate CYP3A inducer in clinical DDI studies.[6,7,8] Rifabutin is an antibacterial agent that is indicated in the treatment of mycobacterial infections, and its active metabolite 25-O-desacetyl-rifabutin contributes to equivalent antimicrobial activity of the parent drug.[9] It is primarily metabolized by CYP3A enzymes and multiple dosing of rifabutin was associated with induction of enzymes of the CYP3A subfamily. Following a single oral dose of 300 mg, rifabutin was readily absorbed with T_{max} range of 2 to 4 hours. Rifabutin was slowly eliminated from plasma, with a mean $t_{1/2}$ of 45 (±17) hours (range: 16 to 69 hours). Although the systemic levels of rifabutin following multiple dosing decreased by 38%, its $t_{1/2}$ remained unchanged.[9]

Rifabutin was found to have a weak induction potential towards CYP2C9 but was not an inducer of P-glycoprotein or organic anion transporting polypeptide.[6] Metabolic induction of CYP3A enzymes are expected to result in decreased plasma concentrations of coadministered drugs that are primarily substrates of and metabolized by CYP3A enzymes, such as zanubrutinib.

Rifabutin was selected in this study as it is more clinically relevant in the target patient population of zanubrutinib (ie, known moderate CYP3A inducers, such as efavirenz and etravirine are indicated for treatment of HIV infection, and HIV patients are excluded from zanubrutinib clinical trials). Rifabutin is a first-line therapeutic alternative to rifampin (ie, due to intolerance to or unacceptable interactions with medication coadministered with rifampin) in the treatment of drug-sensitive tuberculosis.[5] With rifampin being a potent CYP3A inducer, evaluating the PK of zanubrutinib coadministered with rifabutin would be meaningful to determine if dose adjustments should be considered when zanubrutinib is coadministered with drugs that are moderate CYP3A inducers.

3.4. Selection of Doses in the Study

A dose of 320 mg zanubrutinib, which was also administered in the rifampin DDI study (BGB-3111-104), has been chosen for this study to provide a direct comparison of the effect of strong versus moderate CYP3A induction. A dose of 320 mg QD was administered to patients in Phase 1 study BGB-3111-AU-003 and was well tolerated. A single dose of 320 mg was also administered to healthy subjects in the dedicated food effect study

BGB-3111-103 and absorption, metabolism, and excretion study BGB-3111-105, and has been shown to be safe and well tolerated in these studies.

Given the objective of determining whether a moderate CYP3A inducer has an effect on the zanubrutinib PK, this dose is considered to be adequate to achieve study objectives with minimal risk to subjects.

As per FDA guidance for DDI studies[10], a single-dose study design is being used, as zanubrutinib PK in the clinically relevant dose range is linear, with single-dose PK allowing prediction of multiple-dose PK.

Clinically recommended doses of rifabutin (300 mg QD) will be used during this study. Rifabutin will be administered QD for 8 days prior to coadministration with zanubrutinib in order to achieve stable induction of CYP3A.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males of any race, between 18 and 65 years of age, inclusive.
2. Body mass index between 18.0 and 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECGs, vital sign measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, Gilbert's syndrome] is not acceptable) at screening or check-in as assessed by the investigator (or designee).
4. Male subjects are eligible if vasectomized or if they agree to the use of barrier contraception with other highly effective methods, described in Section 6.6, during the study treatment period and for ≥90 days after the last dose of zanubrutinib. Males will also agree to refrain from donating sperm from the time of the first dose of zanubrutinib until ≥90 days after the last dose of zanubrutinib.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder that, in the investigator's judgment, could interfere with the interpretation of the study results.
2. Evidence of any infections (bacterial, viral, fungal, parasitic) within 4 weeks prior to the first dose of study drug, as determined by the investigator (or designee).
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).

4. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (appendectomy and hernia repair will be allowed).
5. Inability to swallow capsules.
6. History or presence of an abnormal ECG prior to the first dose of the study drug that, in the opinion of the investigator (or designee), is clinically significant.
7. History of prolonged QT interval/QT interval corrected for heart rate, with QT interval corrected for heart rate using Fridericia's method (QTcF) >450 msec.
8. History or presence of atrial fibrillation or other significant arrhythmia.
9. Abnormal liver function tests, as defined by aspartate aminotransferase, alanine aminotransferase, or total bilirubin >1.5 × upper limit of normal (ULN) range, confirmed by repeat, at screening or check-in.
10. White blood cell count, neutrophil count, lymphocyte, or platelet count below the lower limit of normal or hemoglobin <10 g/dL, confirmed by repeat, at screening or check-in.
11. Lipase value >1.5 × ULN, confirmed by repeat, at screening or check-in.
12. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 at screening, determined by use of the Modification of Diet in Renal Disease equation.
13. History of alcoholism or drug/chemical abuse within 1 year prior to check-in.
14. Positive urine drug screen at screening or check-in, or positive alcohol test result at check-in.
15. Positive hepatitis panel and/or positive HIV test (Appendix 2). Subjects whose hepatitis panel results are compatible with prior immunization and not infection may be included at the discretion of the investigator.
16. Participation in a clinical study involving administration of an investigational drug (new chemical entity) or use of an experimental medical device in the past 30 days or 5 half-lives, whichever is longer, prior to check-in.
17. Use or intended use of any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's Wort, within 30 days prior to check-in, unless deemed acceptable by the investigator (or designee).
18. Use or intended use of any prescription medications/products, including oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives, within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intended use of slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use or intended use of any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator (or designee).

21. Receipt or intended receipt of any live vaccine within 4 weeks prior to the first dose of study drug or other non-live vaccine within 7 days prior to the first dose of study drug.
22. Use of tobacco- or nicotine-containing products within 3 months prior to check-in.
23. Receipt of blood products within 2 months prior to check-in.
24. Donation of blood from 8 weeks prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
25. Poor peripheral venous access.
26. Major surgical procedure or significant traumatic injury within 14 days prior to check-in or anticipation of the need for major surgery during the study.
27. Inability to reside at the CRU and/or inability to be available for protocol-required procedures or follow-up assessments.
28. Any other unspecified reason that, in the opinion of the investigator (or designee) or sponsor, would make the subject unsuitable for enrollment.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator
- any clinically relevant sign or symptom that, in the opinion of the investigator, warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 5). Other procedures may be performed at the investigator's and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator may also request that the subject

return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the condition stabilizes or is considered chronic or not clinically significant per the investigator, the AE or SAE is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator, sponsor, or sponsor's medical monitor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Zanubrutinib capsules (containing 80 mg zanubrutinib) will be supplied by the sponsor (or designee) along with the batch/lot number. Zanubrutinib will be provided in high-density polyethylene bottles. Zanubrutinib bottles must be stored at room temperature (15°C to 30°C [59°F to 86°F]). The shelf life of zanubrutinib is established based on ongoing stability studies and may be extended during the study. The site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

The investigator (or designee or site) will commercially source rifabutin capsules containing 150 mg. All study drugs will be stored according to the manufacturers' instructions.

Study drugs will be stored at the study site in a location that is locked with restricted access and kept under physical conditions that are consistent with study drug-specific requirements.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The label will include, at a minimum, drug name, dose strength, contents, sponsor, protocol number, lot/batch number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the subject number and name of the investigator. The study drugs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

5.2. Study Treatment Administration

All subjects will receive each of the following treatments:

- single dose of 320 mg zanubrutinib, given orally as 4 × 80-mg capsules in the fasted state, on Days 1 and 11
- 300 mg rifabutin QD, given orally as 2 × 150-mg capsules with food on Days 3 to 10 and in the fasted state on Day 11.

See Section 6.2 for fasting requirements and water restrictions.

Each dose of zanubrutinib and rifabutin will be administered orally with approximately 240 mL of room temperature water. When zanubrutinib and rifabutin are administered concurrently, an additional amount (up to 240 mL) of room temperature water may be administered.

Subjects will be dosed in numerical order while seated and will not be permitted to lie supine for 2 hours after study drug administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a non-randomized study. The study has a fixed treatment sequence.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dose preparation occasion, an inventory of zanubrutinib and rifabutin will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of zanubrutinib capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject, the date of dispensing, and quantities disposed of or returned to the sponsor. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused zanubrutinib capsules will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

Rifabutin will also be subject to accountability procedures, and the CRU staff will destroy unused supplies at the end of the study.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the follow-up visit unless the investigator and/or sponsor have given their prior consent.

Acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

On PK sampling days (Days 1 and 11), zanubrutinib and rifabutin will be administered following an overnight fast of 8 to 10 hours. Subjects will refrain from consuming water/fluids from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water on an ad libitum basis.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until discharge on Day 13.

Caffeine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 13.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 13.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until discharge on Day 13.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 8 weeks prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 8 weeks after the follow-up visit.

6.6. Contraception

Subjects are required to refrain from donation of sperm from the time of the first dose of zanubrutinib until ≥90 days after the last dose of zanubrutinib.

Subjects enrolled in the study must use barrier contraception with other highly effective methods of contraception if he has a female partner of childbearing potential who is not permanently sterile (via hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) or not postmenopausal.

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal. Contraception methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for ≥90 days after the last dose of zanubrutinib). Total sexual abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and, if used, this method must be used in combination with another acceptable method listed above.

If the subject's female partner is using hormonal contraceptives such as birth control pills or devices, a barrier method of contraception (eg, condoms) must also be used.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood samples (for zanubrutinib assay)
- any other procedures (ECGs will be scheduled before vital sign measurements).

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture at the times indicated in the Schedule of Assessments in Appendix 5. Procedures for collection, processing, and shipping of PK samples will be detailed in a separate document.

The individual blood volume requirement for zanubrutinib is listed in Appendix 3. The total blood volume required for all analyses is presented in Appendix 3.

Leftover plasma samples may be used to characterize any potential metabolite(s) of zanubrutinib.

7.1.2. Analytical Methodology

Plasma concentrations of zanubrutinib will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious AEs (SAEs) are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to study completion. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the CRU and at the follow-up visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from the time of study drug administration until study completion. All SAEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator's opinion of the relationship to study treatment.

All AEs and SAEs recorded during the course of the study will be followed until resolution, the condition stabilizes or is considered chronic or not clinically significant per the investigator, the AE or SAE is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent. This will be completed at the investigator's (or designee's) discretion.

7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 5. Clinical laboratory evaluations are listed in Appendix 2.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol test at the times indicated in the Schedule of Assessments in Appendix 5.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

All clinically significant clinical laboratory results will be reported as AEs by the investigator.

7.2.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 5. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

All clinically significant vital sign measurements will be reported as AEs by the investigator.

7.2.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF >500 msec
- QTcF change from the baseline (predose) >60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

All clinically significant ECG results will be reported as AEs by the investigator.

7.2.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 5.

The full physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed, as necessary, at the discretion of the investigator to evaluate AEs or clinical laboratory abnormalities.

All clinically significant physical examination results will be reported as AEs by the investigator.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 15 subjects will be enrolled to ensure that 12 subjects complete the study.

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.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

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

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of zanubrutinib.

8.3. Pharmacokinetic Analyses

The plasma PK parameters of zanubrutinib following zanubrutinib dosing on Days 1 and 11 will be calculated from zanubrutinib concentration-time profiles using standard noncompartmental methods. Leftover plasma samples may be analyzed for metabolite(s) of interest.

The primary PK parameters are AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, and V_z/F for zanubrutinib. Other PK parameters may be reported but will be regarded as secondary and will not be subject to inferential statistical analysis.

A linear mixed-model analysis will be applied to analyze the log-transformed primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}). The model assumes a fixed effect for treatment and a random effect for subject.

Estimates of geometric mean ratios together with the corresponding 90% confidence intervals will be derived for the comparisons of the PK parameters as follows:

- zanubrutinib plus rifabutin (test-Day 11) versus zanubrutinib alone (reference-Day 1)

8.4. Safety Analysis

A verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms. All treatment-emergent AEs will be summarized. A treatment-emergent AE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days after the last treatment with zanubrutinib or was worsening in severity from baseline (pre-treatment).

Clinical laboratory data with values outside of the normal ranges will be identified. Observed values and changes from baseline laboratory data, vital signs, and ECG results will be summarized by visit.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definitions of an AE or SAE as provided in this protocol.

10.1. Adverse Events

10.1.1. Definition and Reporting of an Adverse Event

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE).

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

10.1.1.1. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. Adverse events and SAEs should be assessed and graded based upon the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

- Grade 4: Life threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 10.6.3.

10.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug, will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes assessment of causality for every SAE prior to transmission of the SAE report/eCRF to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his opinion of causality in light of follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility.

An AE should be considered "related" to study drug if any of the following are met:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the subject's clinical condition or other concomitant AEs).

An AE should be considered "unrelated" to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the study drug and the onset of the AE (eg, the AE occurred either before or too long after administration of the product for it to be considered product-related)
- A causal relationship between the study drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

10.1.1.3. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic or not clinically significant per the investigator, the AE or SAE is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be resent to the sponsor within the timeframes outlined in Section 10.6.1.

10.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 10.1.1) or an SAE (as defined in Section 10.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are

detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life threatening.

NOTE: The term "life threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

The following are NOT considered SAEs:

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
  - Hospitalization for social/convenience considerations is not considered an SAE.
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience.
- Results in disability/incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

10.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the IB.

10.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

10.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study treatment of study drug. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

10.4.2. Eliciting Responses About Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How do you feel?
- Any change in your health since your last visit?
- Have you taken any new medications since your last visit?

10.5. Specific Instructions for Recording Adverse Events and Serious Adverse Events

10.5.1. Death

When recording a death as an SAE, the AE that caused or contributed to the fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death."

10.6. Prompt Reporting of Serious Adverse Events

10.6.1. Timeframes for Submitting Serious Adverse Events

Serious AEs will be reported within 24 hours of first knowledge of the SAE to the sponsor or designee as described in Table 2 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 2: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form

Abbreviation: SAE = serious adverse event

10.6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he is to report the information to the sponsor within 24 hours as outlined above in Section 10.6.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 10.1.1.2.

The sponsor will provide contact information for SAE receipt.

10.6.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 10.6.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB).

All suspected unexpected serious adverse reactions (as defined in Section 10.3) will be submitted to all applicable regulatory authorities and investigators for zanubrutinib studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

10.7. Pregnancy Reporting

If the partner of a male subject becomes pregnant within 90 days after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as an SAE.

10.8. Expedited Reporting to Health Authorities, Investigators, and Institutional Review Boards

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, and IRBs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- Zanubrutinib (BGB-3111) IB
- Local prescribing information for rifabutin.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Lipase Potassium Sodium Total bilirubin[a] Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug screen[c]:**	**Other test[b]**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Cotinine test Alcohol test[d]	Tuberculosis test

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at screening.
[c] Only analyzed at screening and check-in.
[d] Only analyzed at check-in; alcohol test may be urine, breath, or blood test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	12.5	6	75
Serology	10.5	1	10.5
Tuberculosis test	3	1	3
Zanubrutinib pharmacokinetics	2	24	48
Total:			136.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 150 mL.

Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European Directive 2001/20/EC for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with CRU personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving

their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, including but not limited to the IB, this protocol, eCRFs, the investigational drug, and any other study information, as well as all information collected and/or documented during the course of the study, is and remains the sole and exclusive property of the sponsor and will be regarded as confidential during the conduct of the study and thereafter. The investigator (or designee) agrees not to disclose such information in any way to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written permission from the sponsor and shall take all reasonable precautions to prevent any unauthorized disclosure by any employee or agent of the study site.

Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the sponsor or CRO standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the sponsor's organization. Monitors will establish and maintain regular contact between the investigator and the sponsor.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification

- Identify any issues and address their resolution.

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his time and the time of his personnel to the monitor to discuss findings and any relevant issues.

Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management department of the CRO.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and prior to any data being entered into the system for any subjects.

The eCRFs should always reflect the latest observations of the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator (or designee) should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data once complete.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible investigator or his designee. The monitor cannot enter data in the eCRFs. Once clinical data have been entered into the eCRF, any corrections or alterations to the data fields will be traceable via an audit trail, meaning that the reason for change, the name of the person who performed the change, together with time and date, will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will respond to any raised queries.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives the investigational product(s), regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique user identification. Specified records will be electronically signed by the investigator to document his review of the data and acknowledgment that the data are accurate. This will be facilitated by means of the investigator's unique user identification and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the MedDRA, Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.0 or higher.

Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and the facilities used for this trial and to allocate his time and the time of his personnel to the auditor/inspector to discuss findings and any relevant issues.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant EDC system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the sponsor retains all rights to publish or not publish the results.

Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.
These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archiving at an off-site facility and transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, arrangements must be made between the investigator and sponsor to store these in secure containers outside of the study center so that they can be returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the study center.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by the site's IRB.

Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

Appendix 5: Schedule of Assessments

Schedule of Assessments

	Screening	Check-in	Treatment Period												Discharge	Follow-up Visit or ET[a]
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	19 (± 1 day)
Procedure																
Informed Consent	X															
Review Inclusion/Exclusion Criteria	X	X														
Demographics	X															
Medical History	X	X[b]														
Height, Weight, and BMI	X	X[c]														X[c]
Drug Screen (including cotinine)	X	X														
Alcohol Test		X														
Serology	X															
Tuberculosis test	X															
Estimated glomerular filtration rate	X															
Study residency:																
Check-in		X														
Check-out															X	
Nonresidential visit	X															X
Study Drug Administration:																
Zanubrutinib Administration[d]			X										X			
Rifabutin Administration[e]					X	X	X	X	X	X	X	X	X			
Pharmacokinetics:																
PK Blood Samples[f]			X	X									X	X		
Safety assessments:																
Physical Examination		X		X[g]												X
Clinical Laboratory Evaluations[h]	X	X		X	X										X	X
Single Safety 12-lead ECG[i]	X	X	X	X									X	X		X
Vital Signs[j]	X	X	X	X									X	X		X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs and SAEs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic; SAE = serious adverse event.

Note: Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, blood draws.

[a] Subjects who withdraw from the study prior to Day 13 should undergo all follow-up assessments at ET.

[b] Interim medical history update only.

[c] Weight only.

[d] Zanubrutinib is to be administered during the morning of Day 1 and on Day 11 at the same time as the rifabutin dose.

[e] Rifabutin is to be administered once daily on Days 3 through 11. On Day 11, zanubrutinib will be administered at the same time as the dose of rifabutin.

[f] Blood samples for analysis of plasma zanubrutinib will be collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours postdose. The allowed sampling window for PK blood samples will be the following: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints ≤12 hours; ± 30 minutes for sampling timepoint at 24 and 36 hours.

[g] Symptom-directed physical examination.

[h] Collection of blood for clinical chemistry and hematology parameters (fasted at least 8 hours), and urine collection for urinalysis will be performed at screening, check-in, Days 2 and 3, at discharge, and at follow-up (or ET).

[i] Single safety 12-lead ECGs will be collected at screening, check-in, on Days 1 and 11 at predose and 1, 2, 4, and 24 hours postdose, and at follow-up (or ET). All ECGs should be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to vital signs and as close as possible to the scheduled blood draws.

[j] Vital sign measurements (supine blood pressure, supine pulse rate, respiratory rate, and oral body temperature) will be obtained at screening and check-in; on Days 1 and 11 at predose and 1, 2, 4, and 24 hours postdose, and at follow-up (or ET). Vital sign measurements should be carried out after ECGs and prior to and as close as possible to having blood drawn. Blood pressure and pulse rate will be measured using the same arm for each reading after the subject has been supine for at least 5 minutes.

[k] All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from the time of study drug administration until study completion. All SAEs will be recorded from the time the subject signs the informed consent form until study completion.