CLINICAL STUDY PROTOCOL

A Phase 1, Open-Label, Fixed Sequence Drug Interaction Study to Evaluate the Potential Intestinal Inhibitory Effect of Quizartinib on the Pharmacokinetics of a P-gp Substrate Dabigatran Etexilate in Healthy Subjects

Effect of Quizartinib on the Pharmacokinetics of the P-gp Substrate Dabigatran Etexilate

PROTOCOL NUMBER: AC220-A-U104

IND NUMBER: 074552

VERSION 1.0, 04 Aug 2020

DAIICHI SANKYO, INC

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DOCUMENT HISTORY

Version Number	Version Date
1.0	04 Aug 2020

INVESTIGATOR AGREEMENT

A Phase 1, Open-Label, Fixed Sequence Drug Interaction Study to Evaluate the Potential Intestinal Inhibitory Effect of Quizartinib on the Pharmacokinetics of a P-gp Substrate Dabigatran Etexilate in Healthy Subjects

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo, Inc representative listed below.

PPD	PPD
Print Name	**Signature** Signing Reason: I approve this document Signing Time: 06-Aug-2020 | 10:50:54 EDT D12BDA0D56B34176AD15179DB7B282ED
Director, Quantitative Clinical Pharmacology	06-Aug-2020 | 10:50:58 EDT
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

PPD	PPD
Print Name	**Signature** Signing Reason: I approve this document Signing Time: 06-Aug-2020 | 09:47:13 CDT 95F1EFC7B2C647B2858EF29F19B9BACF
Principal Investigator	06-Aug-2020 | 09:47:18 CDT
Title	**Date (DD MMM YYYY)**

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
A Phase 1, Open-Label, Fixed Sequence Drug Interaction Study to Evaluate the Potential Intestinal Inhibitory Effect of Quizartinib on the Pharmacokinetics of a P-gp Substrate Dabigatran Etexilate in Healthy Subjects
Protocol Short Title
Effect of Quizartinib on the Pharmacokinetics of the P-glycoprotein (P-gp) Substrate Dabigatran Etexilate
Protocol Number
AC220-A-U104
Sponsor/Collaborators
Daiichi Sankyo, Inc.
Registry Identification(s)
• NCT Number: NCT04459585
IND Number
074552
Study Phase
Phase 1
Planned Geographical Coverage, Study Sites and Location
United States, 1 site, San Antonio, Texas
Study Population
Healthy males and females 18 to 55 years of age (inclusive) with a body mass index (BMI) of 18 kg/m^2 to 32 kg/m^2 (inclusive) at Screening. Females must not be pregnant or lactating.
Study Objectives/Outcome Measures and Endpoints

The table below lists primary and secondary study objectives and endpoints which have outcome measures.

Objectives	Outcome Measure	Category
Primary		
Evaluate the effect of quizartinib on the pharmacokinetics (PK) of dabigatran.	Single dose PK parameters of dabigatran (measured as total and free dabigatran) with and without concomitant administration of quizartinib, to include: Cmax), AUClast, and AUCinf.	PK
Secondary		
Evaluate the PK profile of dabigatran (measured as total and free dabigatran) administered alone and concomitantly with quizartinib.	Single dose PK parameters of dabigatran in Period 1 (administered alone) and Period 2 (administered with quizartinib), to include: Tmax, t1/2.	PK

Evaluate the PK profile of single dose quizartinib administered in the presence of dabigatran etexilate.	Single dose PK parameters of quizartinib, including but not limited to, Cmax, Tmax, and AUClast,74, as applicable.	PK	
Evaluate the PK profile of the metabolite AC886 after single dose administration of quizartinib in the presence of dabigatran etexilate.	Single dose PK parameters of AC886, including but not limited to, Cmax, Tmax, and AUClast,74, as applicable.	PK	
Evaluate the safety and tolerability of quizartinib administered in the presence of dabigatran etexilate.	Occurrence of treatment-emergent adverse events (TEAEs); clinically significant changes in laboratory assessments, triplicate 12-lead electrocardiogram (ECG) evaluations, and vital signs.	Safety	

Study Design

This is a Phase 1, open-label, 2-period, fixed-sequence, drug-drug interaction (DDI) study designed to evaluate the effect of a single oral dose of 60 mg quizartinib on the PK of a single oral dose of 150 mg dabigatran etexilate in maximum of 20 healthy male and female subjects. There will be 2 treatment periods; all subjects will receive dabigatran etexilate only in Period 1 (Reference Treatment) and quizartinib 2 hours prior to dabigatran etexilate administration in Period 2 (Test Treatment).

Following a Screening Period of up to 21 d where subject eligibility will be confirmed, subjects will be admitted to the clinical research unit (CRU) on the day prior to dosing (Day -1) and remained domiciled in the CRU for the duration of the study. At CRU admission, eligibility will be reconfirmed and baseline safety evaluations, including ECGs recorded in triplicate will be assessed.

On the morning of Day 1 of Period 1, a single dose of 150 mg dabigatran etexilate will be orally administered as one 150 mg capsule to subjects in the fasted state (after at least a 10-hour fast) with approximately 240 mL of water. Subjects will continue to fast for at least 4 hours after dosing. Water should be restricted 1 hour before and 1 hour after dosing and allowed ad libitum outside of this window. Serial blood samples for PK analysis will be taken at: predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours post-dabigatran etexilate dose. Safety evaluations (adverse events [AEs], clinical labs, concomitant medication, triplicate ECGs, and vital signs) will be collected through 72 hours after dosing. Safety assessments occurring from the administration of dabigatran etexilate in Period 1 will be attributed to dabigatran etexilate only.

Dose administration in Period 1 and in Period 2 will be separated by approximately 96 hours, with subjects remaining in the CRU.

In Period 2, on the morning of Day 5, a single oral dose of 60 mg quizartinib (two 30 mg tablets) will be given 2 hours prior to administration of a single oral 150 mg dabigatran etexilate (one 150 mg capsule) dose to subjects in the fasted state (after at least a 10 hours fast) with approximately 240 mL of water. Subjects will continue to fast for at least 6 hours after dosing with quizartinib (4 hours after dosing with dabigatran etexilate). Water should be restricted 1 hour before and 1 hour after dosing for each drug (eg, in Period 2, 1 hour before and 3 hours after dosing with quizartinib) and allowed *ad libitum* outside of this window. Subjects will follow a standardized meal schedule outside of the fasting window.

Serial blood samples for PK analysis in Period 2 will be taken relative to quizartinib dosing at: predose and 1, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 26, 38, 50, 62, and 74 hours postdose. The PK of dabigatran etexilate will be determined through 72 hours post-dabigatran etexilate dose, and the PK of quizartinib will be determined through 74 hours post quizartinib dose. Safety evaluations (AEs, triplicate ECGs, clinical labs, concomitant medication, and vital signs) will be collected throughout the study period. ECGs recorded in triplicate will be recorded in Periods 1 and 2 (with 3 separate ECGs at least 2 minutes apart and the average of the 3 QT interval corrected with Fridericia's formula (QTcF) determinations used to determine safety parameters). On Day 1 of Period 1, triplicate ECGs will be recorded within 1 hour prior to dabigatran etexilate administration and at 2 and 6 hours after dabigatran etexilate administration. On Day 5, triplicate ECGs will be recorded within 1 hour prior to quizartinib administration and at 2, 4, and 8 hours after quizartinib administration.

Subjects will be discharged from the CRU and from the study at end of study (EOS) on Day 12 after study procedures are completed. Subjects may be discharged from the CRU post Day 7 of quizartinib dosing if safety parameters are acceptable to the investigator. Completion of all planned assessments through CRU discharge will be considered the EOS.

Study Duration

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed.

Anticipated total duration of the study, excluding screening, is approximately 12 days.

Key Eligibility Criteria

Key Inclusion Criteria:

Subjects eligible for inclusion in this study must meet all inclusion criteria for this study. Below is a list limited to the key inclusion criteria:

- Healthy male and female subjects 18 to 55 years of age (inclusive), at the time of consent with a BMI of 18 kg/m^2 to 32 kg/m^2, inclusive, at Screening.
- Determined to be healthy by the investigator based on medical history, medical examination, vital signs, and 12-lead ECG during Screening and through Day -1.
- Clinical laboratory findings are within normal range or if outside the normal range, deemed not clinically significant in the opinion of the investigator and the Sponsor medical monitor during Screening and on Day -1; Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) and estimated creatinine clearance (CrCl) ≥ 80 mL/min according to the Cockcroft-Gault equation, at Screening and on Day -1.
- Willingness to consume high-potassium foods, such as bananas, cantaloupe, oranges (excluding blood orange), orange juice (excluding blood orange juice), and yogurt, for at least 24 hours before quizartinib administration on Day 5 (except during the fasting period).
- Serum potassium, magnesium, and calcium (corrected for albumin level) within normal limits. Subjects with values below normal at Screening or on Day -1 may be eligible if levels of these electrolytes were corrected before quizartinib administration.
- Serum total bilirubin, alanine aminotransferase, and aspartate aminotransferase not above ULN at Screening or on Day -1. Values above the ULN may be acceptable if not clinically significant, with the Sponsor's agreement.
- Hemoglobin, platelets, and absolute neutrophil count within normal limits at Screening or on Day -1. Hemoglobin below the lower limit of normal may be acceptable if not clinically significant, with the Sponsor's agreement.

Key Exclusion Criteria:

Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key exclusion criteria:

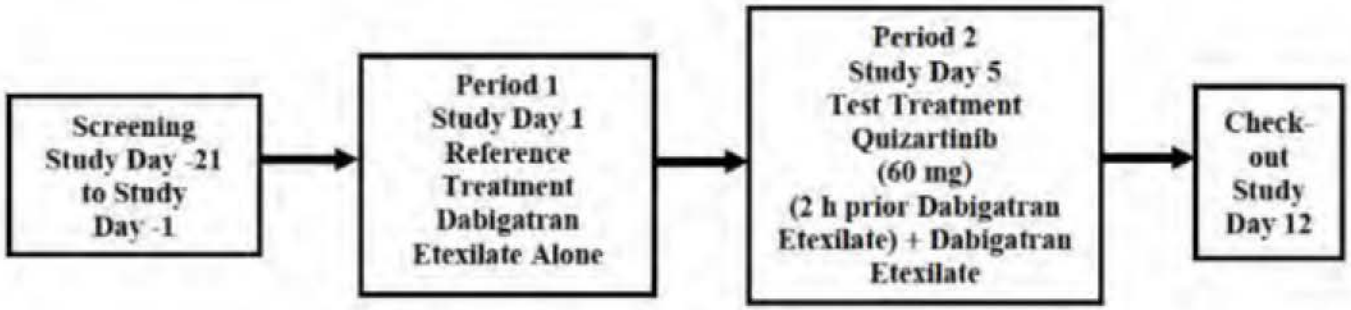
- Any condition that may affect drug absorption, distribution, metabolism, and excretion.
- History of clinically significant drug allergy.
- Known hypersensitivity to quizartinib, dabigatran etexilate, or their excipients.
- Treatment with any investigational product in a clinical study within 30 days (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 30 days) of Day -1.
- Major surgery within 90 days of Day -1.
- Use of prescription medications including hormonal contraceptives, over-the-counter (OTC) medications, medical marijuana, herbal products, or dietary supplements, other than vitamins and minerals generally consistent with daily requirements, within 14 days of Day -1 (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 14 days).

• History, or presence in the average of triplicate ECGs at Screening and Day -1, of any of the following cardiac conduction abnormalities:
  • QTcF >450 ms
  • Evidence of second- or third-degree atrioventricular block
  • Evidence of complete left or right bundle branch block
  • QRS or T wave morphology that could, in the investigator's opinion, render QT interval assessment unreliable (confirmed with triplicate ECG)
• Use of drugs with a risk of QT interval prolongation or Torsades de Pointes within 14 days of Day -1 (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 14 days).

Investigational Medicinal Product, Dose and Mode of Administration
Quizartinib oral tablet, 30 mg Dose = 60 mg (2 × 30 mg) single dose on Day 5 Dabigatran etexilate oral capsule, 150 mg Dose = 150 mg single dose on Day 1 and Day 5
Active Ingredient(s)/INN
Quizartinib hydrochloride
Planned Sample Size
The number of subjects was not based on statistical power considerations; however, a target sample size of 20 was calculated to provide 90% confidence that the estimated ratios (with and without quizartinib) of dabigatran geometric mean Cmax and AUC values would be within 10% of true population values. The calculation assumed that AUC and Cmax were log-normally distributed with a within subject coefficient of variation (CV%) of <30% for AUC and Cmax.

1.2. Study Schema

Figure 1.1: Overview of Study Design



1.3. Schedule of Events

Table 1.1: Schedule of Events

		Screening		Period 1[a]		Period 2[a]				
Overall Study Day		**-21 to -2**	**-1**	**1**	**2 to 5**	**5 to 7**	**8**	**9**	**10 to 11**	**12/ET/ EOS**
Informed Consent[b]		X								
Inclusion/Exclusion Criteria	Demographic Information	X								
	Medical History	X	X							
	Drugs of Abuse[c]	X	X							
	Pregnancy Test[d]	X	X							X
	FSH[e]	X								
	HIV Ab Test	X								
	HBsAg, HCV Ab	X								
	Prior medications	X	X							
PGx	Collect PGx Sample			X						
Vital/ Physical	Physical Examination	X	X			X				X
	Vital Signs[f]	X	X	X		X				X
	Height	X								
	Weight/BMI[g]	X	X							X
Safety	Clinical Labs[h]	X	X			X		X		X
	Triplicate ECG[i]	X	X	X		X				X
Study Drug	Dabigatran etexilate[j]			X		X				
	Quizartinib[k]					X				
PK Blood Sample				X[l]	X[l]	X[m]	X[m]			
Adverse Events		*Continuous*								
Concomitant Medications		*Continuous*								
Clinic	Clinic Admission		X							
	Clinic Discharge									X

Ab = antibody; aPTT = activated partial thromboplastin time; CrCL = creatinine clearance; CRU = clinical research unit; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle stimulating hormone; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human

immunodeficiency virus; INR = international normalized ratio; PGx = pharmacogenomics; PK = pharmacokinetics; QTcF = QT interval corrected with Fridericia's formula

a. Period 1 ends at the collection of clinical laboratory sample (approximately 96 hours post Day 1 dosing) on Day 5. Period 2 starts on Day 5 with the Predose safety sample. The post dose clinical laboratory sample on Day 5, Period 1 (approximately 96 hours post Day 1 dosing) can be also be used as a pre-dose clinical laboratory sample for Period 2.
b. Signed written informed consent prior to any study procedures.
c. Urine test for drugs of abuse (illegal and/or prescription), including tobacco and alcohol will be tested during Screening and Day-1.
d. Serum pregnancy test at Screening; urine pregnancy test at CRU admission (Day -1), and on Day 12 (ET/EOS).
e. Naturally postmenopausal female subjects only.
f. Vital signs should be taken at Screening, at CRU admission (Day -1), prior to administration of dabigatran etexilate (Day 1) and 2 hours after dabigatran etexilate dosing, on Day 12 (ET/EOS), and as clinically indicated. Vital signs should be taken predose, postdose 2 hours and 6 hours after dabigatran etexilate administration on Day 1 and on Day 5. Vital signs should be taken at 1 hour prior to quizartinib administration and at 2, 4, and 8 hours post quizartinib administration. Blood pressure and pulse rate will be measured after the subject has rested in a supine position for at least 5 minutes or more and prior to laboratory draws and taken after at least a 5-10 minutes supine rest at all ECG time points.
g. BMI at screening only.
h. Clinical labs (hematology, clinical chemistry, aPTT/PT/INR, CrCL and urinalysis) should be taken at Screening, Day -1, approximately 96 hours post dosing on Day 5 (Period 1), on Day 9 and on Day 12 (ET/EOS). Subjects will have to fast (except water) for at least 10 hours before having blood drawn for these laboratory tests.
i. 12-lead ECG should be recorded in triplicate with the clinical site's equipment (3 separate ECGs at least 2 minutes apart; the average of the 3 QTcF determinations used to determine safety parameters). ECGs should be obtained once, in triplicate, at Screening, on Day -1, and on Day 12 (ET/EOS). The ECG will be measured after the subject has rested in a supine position for 5 minutes or more. On Day 1 of Period 1, triplicate ECGs will be recorded within 1 hour prior to dabigatran etexilate administration and at 2 and 6 hours after dabigatran etexilate administration. On Day 5 of Period 2, triplicate ECGs should be recorded within 1 hour prior to quizartinib administration and 2, 4, and 8 hours after quizartinib administration.
j. Dabigatran etexilate will be administered on Day 1 and Day 5
k. Quizartinib should be administered 2 hours prior to dabigatran etexilate.
l. Blood for PK analysis should be taken in Period 1: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dabigatran dose.
m. Blood for PK analysis should be taken in Period 2 (relative to quizartinib): predose and 1, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 26, 38, 50, 62, and 74 hours post-quizartinib dose.

2. INTRODUCTION

2.1. Background

Quizartinib is a novel oral Class III receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective but reversible inhibition of Feline McDonough sarcoma (FMS)-like tyrosine kinase 3 (FLT3). At clinically relevant concentrations, quizartinib also binds to KIT proto-oncogene receptor tyrosine kinase (KIT) (another RTK), but with lower affinity than to FLT3, and has little or no affinity for other RTKs. Quizartinib has been approved in Japan for the treatment of adult patients with relapsed/refractory FTL3-ITD-positive acute myeloid leukemia (AML). Currently quizartinib is being studied alone or in combination with other agents as a treatment for AML and myelodysplastic syndrome (MDS) in adult and pediatric populations.

Following oral administration, the peak exposure of quizartinib and its major active metabolite, (AC886) occurs at a median of approximately 4 hours (range: 2 hours to 8 hours) and 5 hours (range: 4 hours to 120 hours) postdose, respectively. The plasma exposure of quizartinib and AC886 increased proportional with the dose of quizartinib over a dose range of 20 mg to 90 mg. At steady state, AC886 exposure was approximately 60% of the parent steady state exposure. In vitro reaction phenotyping using human liver microsomes and recombinant human CYP enzymes showed that both quizartinib and AC886 are primarily metabolized by CYP3A and have estimated effective half-lives (t1/2) of 73 hours and 119 hours, respectively. Additionally, AC886 is also formed from quizartinib by CYP3A.

In a previously conducted dedicated hepatic impairment (HI) study in subjects with mild and moderate HI as defined by Child-Pugh score, quizartinib exposure increased approximately 30% and 15% increase in AUCinf, respectively. The total active exposure (AUC) of quizartinib plus AC886 increased in subjects with mild HI by 17%, which was not considered clinically meaningful. Quizartinib can be administered with pH-modifying drugs such as proton pump inhibitors, H2 antagonists, or antacids, and without regard to food. Strong CYP3A inhibitor (ketoconazole) and moderate CYP3A inhibitor (fluconazole) increased quizartinib AUC by 94% and 20%, respectively. Strong CYP3A inducer rifampin decreased quizartinib AUC by approximately 70%; however, due to bioanalytical issue, the results were not quantitatively conclusive.

This is a Phase 1, open-label, 2-period, fixed-sequence study in 20 healthy male and female subjects designed to evaluate the effect of a single oral dose of 60 mg quizartinib on the pharmacokinetics (PK) of dabigatran after a single oral dose of 150 mg dabigatran etexilate.

2.2. Study Rationale

The rationale for this study is to evaluate the potential of quizartinib to inhibit intestinal P-glycoprotein (P-gp) transport of the P-gp substrate dabigatran etexilate.

The IC_{50} values of quizartinib and its major circulating AC886 for P-gp transporter were 9.55 µM and >30 µM, respectively, from in vitro studies in MDCKII-MDR1 cells. Systemic P-gp inhibition is not expected as quizartinib is >99% bound to plasma proteins and is below the

cutoff defined in the EMA guideline on the investigation of drug interactions. However, there is the potential for P-gp inhibition in the intestine by quizartinib since concentrations in the gut (Ig) relative to the P-gp IC50 exceeds the cutoff criteria (Ig/IC50 = 39.7 >10).

Dabigatran etexilate is a P-gp substrate, which after oral administration is converted to dabigatran. The hydrolyzed active moiety dabigatran is not a P-gp substrate. Dabigatran is further metabolized to form glucuronide conjugates. As quizartinib has the potential to inhibit intestinal P-gp at the clinical dose, effect of quizartinib on an intestinal-specific P-gp substrate dabigatran etexilate will be evaluated in this study.

2.3. Benefit and Risk Assessment

This is a Phase 1 study being conducted in healthy subjects, and, as such, no benefit to the subjects from either dabigatran etexilate or quizartinib is intended or expected.

In clinical program, a total of 1,881 subjects had received quizartinib in 23 studies: 1,396 subjects with AML, 13 subjects with solid tumors, and 472 healthy subjects. In addition, 777 subjects have been treated in 6 investigator-initiated studies. The dose of quizartinib administered in these studies ranged from 12 mg to 450 mg with treatment duration up to 169 weeks. Out of 472 healthy subjects, 307 subjects received single dose of quizartinib. Toxicities observed for quizartinib in healthy subjects (n = 307) following single dose administration were headache (6.8% subjects), upper respiratory tract infection (2.6% subjects), and diarrhea (2.0% subjects). QT prolongation and combined elevations of alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) and total bilirubin (TBil) >2 × ULN are the two adverse events of special interest (AESI) following quizartinib dosing. In approximately 3% of patients with AML in a Phase 3 clinical study with repeated daily dosing the corrected QT interval (QTc) interval was prolonged to more than 500 milliseconds (ms).

Of the 241 subjects treated with quizartinib monotherapy in the completed Phase 3 clinical study in adults with relapsed/refractory AML (Study AC220 007), 3.3% were found to have a QT interval corrected with Fridericia's formula (QTcF) interval greater than 500 ms, and 12.4% had an increase from baseline QTcF greater than 60 ms based on central review of electrocardiogram (ECG) data; there were no cases of Torsades de Pointes (TdP), cardiac arrest, or sudden death reported. One reported case of ventricular tachycardia was not associated with QTc prolongation and did not require cardiac intervention. In the remaining completed monotherapy studies in the treatment of relapsed or refractory AML there was: 1 subject in a Phase 2 clinical study who developed non-fatal TdP while receiving a dose of 90 mg, and the event resolved following discontinuation of quizartinib; and one event of fatal cardiac arrest where a potential arrhythmia event cannot be excluded.

In clinical studies to date, the most common serious adverse reactions are myelosuppressive in nature and include infections, febrile neutropenia, and bleeding. Overall, the most common adverse reactions also included nausea, asthenic conditions, pyrexia, vomiting, and diarrhea. Further, there is a clear association between quizartinib and QT prolongation which occurs in a dose dependent manner. Risk management for QT prolongation in the multiple dose studies includes ECG (QTcF) based dose modifications (including dose escalation, dose interruption, dose reduction and dose discontinuation) as well as correction of electrolytes. In summary, the AEs observed with quizartinib treatment could be managed by monitoring, dose modifications,

and/or standard supportive therapies. Overall, quizartinib treatment was well tolerated at the proposed dose and dose regimen in adults with RR AML with FLT3-ITD. Furthermore, based on the results of the Transgenic Rat Mutation Assay (TGR) quizartinib is not mutagenic and can be dosed in healthy subjects (report ongoing).

Please refer to the most current version of the prescribing information for the risks associated with dabigatran etexilate and the most updated version of the Investigator's Brochure (IB) for the risks associated with quizartinib.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

3.1. Primary Objective/Endpoint

The primary objective of this study is:

- To evaluate the effect of quizartinib on the PK of dabigatran.

The primary endpoint of this study is:

- Single dose PK parameters of dabigatran (measured as total and free dabigatran) with and without concomitant administration of quizartinib, to include: Cmax, AUClast, and AUCinf.

3.2. Secondary Objectives/Endpoints

The secondary objectives of this study are:

- To evaluate the PK profile of dabigatran (measured as total and free dabigatran) administered alone and concomitantly with quizartinib.
- To evaluate the PK profile of single dose quizartinib administered in the presence of dabigatran etexilate.
- To evaluate the PK profile of the metabolite AC886 after single dose administration of quizartinib in the presence of dabigatran etexilate.
- To evaluate the safety and tolerability of quizartinib administered in the presence of dabigatran etexilate.

The secondary endpoints of this study are:

- Single dose PK parameters of dabigatran in Period 1 (administered alone) and Period 2 (administered with quizartinib), to include: Tmax, t1/2.
- Single dose PK parameters of quizartinib, including but not limited to, Cmax, Tmax, and AUClast,74, as applicable.
- Single dose PK parameters of AC886, including but not limited to, Cmax, Tmax, and AUClast,74, as applicable.
- Occurrence of treatment-emergent adverse events (TEAEs); clinically significant changes in laboratory assessments, triplicate 12-lead ECG evaluations, and vital signs.

3.3. Rationale for Selection of Primary and Key Secondary Endpoints

The objectives and endpoints selected for this study are consistent with those used for determination of drug-drug interaction (DDI) studies.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, 2-period, fixed-sequence, DDI study in healthy male and female subjects designed to evaluate the effect of a single oral dose of 60 mg quizartinib on the PK of a single oral dose of 150 mg dabigatran etexilate. The subject population is described in Section 5. A flow diagram of study activities is presented in Figure 1.1 .

4.1.1. Design Overview

A maximum of 20 eligible healthy subjects will be enrolled. There will be 2 treatment periods; all subjects will receive dabigatran etexilate in Period 1 (Reference Treatment) and quizartinib 2 hours prior to dabigatran etexilate administration in Period 2 (Test Treatment).

Following a Screening Period of up to 21 days where subject eligibility will be confirmed, subjects will be admitted to the clinical research unit (CRU) on the day prior to dosing (Day -1) and remained domiciled in the CRU for the duration of the study. At CRU admission, eligibility will be reconfirmed and baseline safety evaluations, including ECGs recorded in triplicate will be assessed.

4.1.2. End-of-Study

Subjects will be discharged from the CRU and from the study at end of study (EOS) on Day 12 after study procedures are completed. Subjects may be discharged from the CRU post Day 7 of quizartinib dosing if safety parameters are acceptable to the investigator. Completion of all planned assessments through CRU discharge will be considered the EOS. Study visits and assessment timing are outlined in Table 1.1.

4.1.3. Dose Regimen

On the morning of Day 1 of Period 1, a single dose of 150 mg dabigatran etexilate will be orally administered as one 150 mg capsule to subjects in the fasted state (after at least 10 hours fast) with approximately 240 mL of water. Subjects will continue to fast for at least 4 hours after dosing. Water should be restricted 1 hour before and 1 hour after dosing and allowed ad libitum outside of this window. Serial blood samples for PK analysis will be taken at: predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours post-dabigatran etexilate dose. Safety evaluations (adverse events [AEs], clinical labs, concomitant medication, triplicate ECGs, and vital signs) will be collected through 72 hours after dosing. Safety assessments occurring from the administration of dabigatran etexilate in Period 1 will be attributed to dabigatran etexilate only.

Dose administration in Period 1 and in Period 2 will be separated by approximately 96 hours, with subjects remaining in the CRU.

In Period 2, on the morning of Day 5, a single oral dose of 60 mg quizartinib (two 30 mg tablets) will be given 2 hours prior to administration of a single oral 150 mg dabigatran etexilate (one 150 mg capsule) dose to subjects in the fasted state (after at least 10 hours fast) with approximately 240 mL of water. Subjects will continue to fast for at least 6 hours after dosing with quizartinib (4 hours after dosing with dabigatran etexilate).

Water should be restricted 1 hour before and 1 hour after dosing for each drug (eg, in Period 2, 1 hour before and 3 hours after dosing with quizartinib) and allowed ad libitum outside of this window. Subjects will follow a standardized meal schedule outside of the fasting window.

Serial blood samples for PK analysis in Period 2 will be taken relative to quizartinib dosing at: predose and 1, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 26, 38, 50, 62, and 74 hours postdose. The PK of dabigatran will be determined through 72 hours post-dabigatran dose, and the PK of quizartinib will be determined through 74 hours post quizartinib dose.

Safety evaluations (AEs, triplicate ECGs, clinical labs, concomitant medication, and vital signs) will be collected throughout the study period. ECGs recorded in triplicate will be recorded in Periods 1 and 2 (with 3 separate ECGs at least 2 minutes apart and the average of the 3 QTcF determinations used to determine safety parameters). On Day 1 of Period 1, triplicate ECGs will be recorded within 1 hour prior to dabigatran etexilate administration and at 2 and 6 hours after dabigatran etexilate administration. On Day 5, triplicate ECGs will be recorded within 1 hour prior to quizartinib administration and at 2, 4, and 8 hours after quizartinib administration.

4.1.4. Duration

Anticipated total duration of the study, excluding screening, is approximately 12 days. The study overall will be completed when the last datapoints for primary and secondary endpoints are collected and recorded.

4.2. Justification for Dose

In this study, subjects will be given quizartinib as two 30 mg tablets (60 mg total dose) under fasted conditions. This is the highest proposed clinical dose of quizartinib which is being investigated in the first line treatment for AML (QuANTUM-First study) and the highest clinical dose approved in Japan for the treatment of adult patients with relapsed/refractory FTL3-ITD-positive AML. Single doses of up to 90 mg have been administered to healthy subjects in a prior study (AC220-014) and are well tolerated.

The highest approved clinical dose of dabigatran etexilate is 150 mg. Therefore, the effect of quizartinib on dabigatran etexilate will be assessed at a dose of 150 mg.

5. STUDY POPULATION

This Phase 1 study is being conducted in healthy subjects.

5.1. Inclusion Criteria

Subjects eligible for inclusion in this study have to meet all inclusion criteria for this study.

1. Voluntarily consents to participate in this study and provides written informed consent before the start of any study-specific procedures.
2. Male and female subjects 18 to 55 years of age, (inclusive), with a body mass index (BMI) of 18 kg/m^2 to 32 kg/m^2, inclusive, at Screening.
3. In females, documented surgical sterilization, postmenopausal status for at least 1 year (follicle stimulating hormone [FSH] >40 mIU/mL serum at Screening), or agreement to have sterile male partner, or agreement to use 1 of the protocol-approved means of contraception from Screening until 6 months after the dose of quizartinib. See Section 5.3 Contraception Requirements.
4. In males, documented surgical sterilization, or sexual abstinence, or agreement to use 1 of the protocol-approved means of contraception from Screening until 6 months after the dose of quizartinib. See Section 5.3 Contraception Requirements.
5. In females, must not retrieve eggs/ova via assisted reproductive technology (ART) either for their own use or donation while on study or for 6 months after the last dose of quizartinib, whichever is later.
6. In males, agreement to avoid sperm donation for 6 months after the dose of quizartinib.
7. Determined to be healthy by the investigator based on medical history, medical examination, vital signs, and 12-lead ECG during Screening and through Day -1.
8. Clinical laboratory findings are within normal range or if outside the normal range, deemed not clinically significant in the opinion of the investigator and the Sponsor medical monitor during Screening and on Day -1 Serum creatinine $\leq 1.5 \times$ ULN and estimated creatinine clearance (CrCl) ≥ 80 mL/min according to the Cockcroft-Gault equation, at Screening and on Day -1.
9. Willingness to consume high-potassium foods, such as bananas, cantaloupe, oranges (excluding blood orange), orange juice (excluding blood orange juice), and yogurt, for at least 24 hours before quizartinib administration on Day 5 (except during the fasting period).
10. Serum potassium, magnesium, and calcium (corrected for albumin level) within normal limits. Subjects with values below normal at Screening or on Day -1 may be eligible if levels of these electrolytes were corrected before quizartinib administration.
11. Serum TBil, ALT, and aspartate aminotransferase (AST) not above ULN at Screening or on Day -1. Values above the ULN may be acceptable if not clinically significant, with the Sponsor's agreement.

12. Hemoglobin, platelets, and absolute neutrophil count within normal limits at Screening or on Day -1. Hemoglobin below the lower limit of normal may be acceptable if not clinically significant, with the Sponsor's agreement.

5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria within 21 days prior to Day -1 are not to be enrolled in this study.

Medical History

1. Any condition that may affect drug absorption, distribution, metabolism, and excretion.
2. History of clinically significant drug allergy.
3. Known hypersensitivity to quizartinib, dabigatran etexilate, or their excipients.
4. Major surgery within 90 days of Day -1.
5. History or presence of clinically significant cardiovascular disease, including any of the following:
   - Angina
   - TdP
   - Myocardial infarction
   - Coronary artery disease
   - Cardiomyopathy
   - Congestive heart failure
   - Cardiac valvular disease
   - Dysrhythmias
   - Cardiogenic syncope
   - Hypertension
   - Cerebrovascular accident
   - Transient ischemic attack
   - History of QT interval prolongation
   - Family history of QT interval prolongation
   - Diagnosed or suspected congenital long QT syndrome
6. History, or presence in the average of triplicate ECGs at Screening and Day -1, of any of the following cardiac conduction abnormalities:
   - QTcF >450 ms
   - Evidence of second- or third-degree atrioventricular block
   - Evidence of complete left or right bundle branch block

- QRS or T wave morphology that could, in the investigator's opinion, render QT interval assessment unreliable (confirmed with triplicate ECG)

7. History of any cancer, except non-melanoma skin cancer, or resected non-metastatic cancer with no evidence of disease accepted by the investigator and Sponsor medical monitor.
8. History or family history of bleeding disorders.
9. Presence of mechanical prosthetic heart valves.
10. Evidence of hepatitis B infection or hepatitis C antibody at Screening.
11. History or presence of human immunodeficiency virus (HIV) antibody.
12. Active infection within 30 days of Day -1.
13. Immunization within 30 days of Screening.
14. Inadequate venous access.

Medication Use and Lifestyle

15. Treatment with any investigational product in a clinical study within 30 days (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 30 days) of Day -1.
16. Use of prescription medications including hormonal contraceptives, over-the-counter (OTC) medications, medical marijuana, herbal products (eg, St. John's wort, echinacea, gingko biloba, ginseng, kava kava), or dietary supplements, other than vitamins and minerals generally consistent with daily requirements, within 14 days of Day -1 (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 14 days).

    Note: The use of acetaminophen of less than 2 grams/day and 1% topical hydrocortisone for contact dermatitis are acceptable concomitant therapies at any time during the study. Prune juice and stool softeners for constipation may not be given from 2 days prior to quizartinib dosing through the day of quizartinib dosing, but may be given at any time 24 hours after the dose of quizartinib.
17. Use of drugs with a risk of QT interval prolongation or TdP within 14 days of Day -1 (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 14 days).
18. Consumption of alcohol, xanthine-containing beverages or foods including regular coffee, regular tea, caffeine-containing soft drinks and energy drinks, and chocolate, or blood oranges, grapefruit, grapefruit juice, pomegranates, pomegranate juice, Seville (bitter) oranges, or star fruit within 72 hours of Day -1.
19. Anticipated need for prescription medications, OTC medications, medical marijuana, herbal products, or dietary supplements before study completion. Current or recent (within 30 days of Day -1) use of tobacco or nicotine products (including nicotine patches and/or gum).
20. Recent (within 1 year of Day -1) history of alcohol abuse or illicit drug use.
21. Average consumption of >14 alcoholic drinks per week (where 1 alcoholic drink is defined as (1 drink = 5 ounces of wine, 12 ounces of beer, or 1.5 ounces of hard liquor), or unwillingness to refrain from alcohol consumption during the study.

22. Exposure to quizartinib within 1 year of Day -1.

Laboratory Tests

23. Positive urine test result for illicit drugs during any scheduled test.
24. Significant blood loss, donation of ≥450 mL of blood, or blood or blood product transfusion within 7 days of Day -1. Inability or unwillingness to comply with study restrictions or return to the study site for any necessary blood sampling.
25. Women who are pregnant or breastfeeding.
26. Positive serum pregnancy test result at Screening and urine pregnancy test result at Day -1 or a positive urine pregnancy test at Day -1, or Day 12, prior to CRU discharge.

5.3. Contraception Requirements

Female Subjects

Females of childbearing potential must use contraception while enrolled in this study.

From Screening until 6 months after the dose of quizartinib:

- Sterile male partner
- Any of the following with spermicide:
  - Non-hormonal IUD
  - Female or male condom
  - Contraceptive sponge
  - Diaphragm
  - Cervical cap

Any of the following (hormonal contraceptives may be started only after CRU Discharge [Day 12]. However, one of the non-hormonal methods listed above must be used in conjunction with the hormonal contraceptive for 2 weeks until the hormonal contraceptive becomes effective and then the hormonal contraceptive must be continued until 6 months after the dose of quizartinib:

- Hormonal IUD
- Intravaginal system
- Oral, implantable, transdermal, or injectable contraceptive

Male Subjects

Males of reproductive potential must use contraception while enrolled in this study.

- From Screening until 6 months after the dose of quizartinib:Sterile or postmenopausal female partner
- Male condom with spermicide

- Use of any of the following with spermicide by female partner:
  - Non-hormonal IUD
  - Female condom
  - Contraceptive sponge
  - Diaphragm
  - Cervical cap
- Use of any of the following by female partner:
  - Hormonal IUD
  - Intravaginal system
  - Oral, implantable, transdermal or injectable contraceptive

5.4. Screening Failures, Rescreening, and Subject Replacement

Subjects who withdraw or are withdrawn from the study will not be replaced unless approved by the Sponsor.

6. STUDY TREATMENTS

6.1. Study Drugs Description

Quizartinib is a white to off-white crystalline powder, dichloride salt, administered orally as two 30 mg tablets (60 mg total dose) (26.5 mg free base). Dabigatran etexilate (Pradaxa®) is a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with "R150".

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of quizartinib and dabigatran etexilate.

Table 6.1: Study Drug Dosing Information

Study Drug Name	Quizartinib	Dabigatran Etexilate
Dosage Formulation	30-mg tablet[a]	150-mg capsule
Dosage Level(s)	60 mg	150 mg
Route of Administration	Oral	Oral
Dosing	Single dose	Single dose
Duration	Once on Day 5	Once on Day 1 and Day 5
Packaging	Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations	Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations
Labeling	Bottles will be labeled as required per local regulatory requirement	Box of blister cards will be labeled as required per local regulatory requirement

a Each 30-mg tablet contains 30-mg quizartinib dihydrochloride (26.5 mg free base).

Quizartinib will be supplied as tablets and dabigatran etexilate will be supplied as capsules that need no preparation at the study site.

6.2. Preparation, Handling, Storage, and Accountability for Study Drug(s)

6.2.1. Preparation, Handling, and Disposal

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures (SOP) of the site.

6.2.2. Administration

On Day 1 and Day 5, a single oral 150 mg capsule dose of dabigatran etexilate will be administered; on Day 5 a single oral 60 mg dose of quizartinib will be administered as two 30 mg tablets (26.5 mg free base) 2 hours prior to administration of a single oral 150 mg capsule dose of dabigatran etexilate.

6.2.3. Storage

Quizartinib tablets should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F) with allowed excursions between 15°C and 30°C (59°F and 86°F) and protected from light. The storage condition of quizartinib drug bottles must be logged daily. If the storage room/cabinet does not have an automated continuous temperature recording system to record the daily temperature data, daily temperature must be monitored and recorded on a temperature log.

Dabigatran etexilate capsules should be stored at 25°C (77°F) with allowed excursions between 15°C and 30°C (59°F and 86°F) and protected from moisture.

6.2.4. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug against the shipping documentation.

The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the study site.

The investigational pharmacy will maintain a record of study drug inventory.

The investigator or designee will maintain subject ID, bottle number, lot number and date dispensed on a subject study drug dispensing and accountability log.

6.3. Measure to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Allocation

There is no randomization in this study.

6.3.2. Blinding

This is an open-label study. No blinding will be required.

6.4. Treatment Compliance

To ensure treatment compliance, all doses will be administered under the supervision of clinical study personnel. A mouth and hand check must be carried out in all the subjects to ensure that all the study medication has been swallowed.

The exact times of investigational medicinal product (IMP) dosing and the number of units administered will be recorded in the electronic case report form (eCRF).

6.5. Guidelines for Dose Modification

Not applicable. No dose modification will be allowed.

6.6. Prior and Concomitant Medications

All therapies received by subjects within 21 days prior to screening will be recorded as prior therapies.

All therapies used from the time the subject signs the informed consent form (ICF) for study participation to the final study visit will be recorded as concomitant therapies. Any concomitant medications received from screening through the final study visit will be recorded in the eCRF. Concomitant medications and other prescription medications, OTC and herbal products, and dietary supplements, are not permitted unless discussed and allowed by the Sponsor and Medical Monitor.

6.7. Prohibited Therapies/Products

The following (except medications approved by the Sponsor on a case-by-case basis) are prohibited within 14 days (or 5 drug half-lives, if 5 drug half-lives were expected to exceed 14 days) before Day -1 and throughout the study:

- Hormonal contraceptives and all other prescription medications, including CYP3A inducers (Table 10.3), and CYP3A inhibitors (Table 10.2) should be used only if absolutely necessary .
- Medical marijuana
- Melatonin and all other OTC products
- Echinacea, gingko biloba, ginseng, kava kava, St. John's wort, and all other herbal products
- Vitamins and minerals generally consistent with daily requirements are permitted during the 14 days before Day -1. However, all dietary supplements are prohibited starting on Day -1 and throughout the study.
- Blood oranges, grapefruit, grapefruit juice, pomegranates, pomegranate juice, Seville (bitter) oranges, and star fruit are prohibited for 72 hours before Day -1 and throughout the study.
- Alcohol, xanthine-containing beverages, or foods including regular coffee, regular tea, caffeine-containing soft drinks and energy drinks, and chocolate are prohibited for 72 hours before Day -1 and throughout the study.

6.8. Permitted Therapies/Products

The use of acetaminophen of less than 2 grams/day and 1% topical hydrocortisone for contact dermatitis are acceptable concomitant therapies at any time during the study. Prune juice and stool softeners for constipation may not be given from 2 days prior to quizartinib dosing through the day of quizartinib dosing, but may be given at any time 24 hours after the dose of quizartinib.

7. WITHDRAWAL/DISCONTINUATION FROM THE STUDY

7.1. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- AE
- Withdrawal of consent by subject
- Investigator decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Other

7.2. Withdrawal Procedures

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the study physician or at the study site.

If a subject is withdrawn from the study, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures.

See Table 1.1 for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

Subjects will be considered lost to follow-up if he/she leaves the CRU prior to the discharge and is unable to be contacted by the study site staff. Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (by telephone call, texts, emails). These contact attempts should be documented.

8. STUDY PROCEDURES

See Schedule of Events (SoEs), Table 1.1, for the procedures conducted at specific time points during Screening, Period 1, and Period 2.

8.1. Eligibility Assessment

Review the subject's demographics, medical history, vital signs (blood pressure, heart rate, respiratory rate, and temperature), and results of tests (eg, physical examination, ECG, and laboratory assessments) and compare against the eligibility criteria (Section 5 and Section 5.2).

8.2. Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population. See Section 10.1.4 for additional details.

8.3. General Medical History and Baseline Conditions

Subject's medical history will be obtained by the investigator or a qualified designee.

An untoward medical occurrence (including clinically relevant laboratory values/vital signs that are out of range) that is noted prior to the first dose of study medication will be recorded.

8.4. Demographics

Review the subject's demographics against the eligibility criteria.

8.5. Pharmacokinetic/Pharmacodynamic Assessments

8.5.1. Pharmacokinetic Assessment(s)

Pharmacokinetic blood samples will be collected, processed, and shipped as detailed in the SoE and in the Laboratory Processing Specification document Section 10.5.

Allowable time windows for PK blood samples are provided in Section 10.7. Quizartinib and AC886 showed temperature- and concentration-dependent partitioning into blood cells; therefore, blood samples must be processed at room temperature for determination of plasma quizartinib and AC886 concentrations.

8.5.2. Pharmacodynamic Assessment(s)

No pharmacodynamic (PD) assessments are planned for this study.

8.6. Safety Assessments

8.6.1. Reporting of Exposure to COVID-19 (SARS-CoV-2)

All confirmed or suspected coronavirus disease 2019 (COVID-19) events must be recorded in the eCRF.

- Subjects who test positive for COVID-19 should be reported as "Confirmed COVID-19", either as an AE or serious adverse event (SAE).
- Subjects whose medical history and clinical manifestations, signs, and possible exposure are consistent with COVID-19 but for whom no polymerase chain reaction (PCR) or antibody test for COVID-19 is available should be reported as "Suspected COVID-19", either as an AE or SAE.

The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, i.e., the investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.

In the event that the investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious AE in the eCRF.

When assessing the severity of the COVID-19 AE, the severity grading criteria as defined in Section 10.4.3 will be used.

All study drug interruption or dose reduction or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.

For both serious and non-serious COVID-related AEs, the following information should be provided as a minimum:

- Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the laboratory eCRF, if available.
- Clinical course of the case including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID-19, and outcome in relevant eCRF (e.g., concomitant medication, AEs).
- Findings from diagnostic imaging (including computed tomography [CT] scan or other chest imaging).

8.6.2. Adverse Events

AE information should be collected for all enrolled subjects from the date of individual's signed informed consent.

8.6.2.1. Method to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.4. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each

study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue either dabigatran etexilate or quizartinib.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, lead to dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

8.6.2.2. Time Period for Collecting Adverse Events, including AESIs and Serious Adverse Events

All AEs occurring after the subject signs the ICF and up to 30 days after the last dose of study medication whether observed by the investigator or reported by the subject, will be recorded. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

8.6.2.3. Reporting Procedure for Investigators

All AEs (including AESIs and SAEs) will be reported. All AEs (serious and non-serious) must be reported with the investigator's assessment of seriousness, severity, and causality to either dabigatran etexilate or quizartinib.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

8.6.2.4. Serious Adverse Events Reporting

The following types of events should be reported by the investigator on a serious adverse event report (SAVER) form within 24 hours of awareness:

- SAEs (Section 10.4.2)
- Hepatic events (both serious and non-serious) meeting the laboratory criteria of a potential Hy's Law criteria (as defined in Section 8.6.2.7)
- QTcF prolongation, TdP, and other ventricular arrhythmias (as defined in Section 8.6.2.7)

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Call the local SAE Hotline or your study monitor for any questions on SAE reporting.

See Section 8.6.2.2 for details on the time period for collecting SAEs.

8.6.2.5. Reporting Requirement to Sites and Regulatory Authorities

The investigator must report all SAEs to the Sponsor and may need to report any suspected unexpected serious adverse reactions (SUSARs) occurring at the study site to the Institutional Review Board (IRB).

The Sponsor will comply with any additional local safety reporting requirements. The Sponsor will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB.[1]

8.6.2.6. Follow-up for AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations.

Urgent safety queries must be followed up and addressed promptly. The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.6.2.7. Adverse Events of Special Interest

8.6.2.7.1. Hepatic Events

Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) $\geq 3 \times$ ULN and an elevated TBil $> 2 \times$ ULN that may occur at different time points during the study conduct should always be reported to the Sponsor. These events must be reported with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of Investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 10.2 in order to determine the nature and severity of the potential liver injury.

8.6.2.7.2. QTcF Prolongation, Torsades de Pointes, and Other Ventricular Arrhythmias

Subjects who experience >480 ms QTcF prolongation must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved. QTcF prolongation ≥Grade 3, either serious or non-serious and whether or not causally related, must be recorded as an AE or SAE in the eCRF within 24 hours of the assessment, with the investigator's assessment of seriousness, causality, and a detailed narrative.

Monitoring in subjects with QTcF prolongation will include the following:

- Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects.

8.6.2.8. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to the Sponsor within 24 hours of awareness and recorded via SAVER/overdose form or eCRF.

An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the investigator as clinically relevant, ie, poses an actual or potential risk to the subject. Occupational exposures must be reported via the SAVER form.

8.6.2.9. Pregnancy

It is the responsibility of the investigator or designee to notify the Sponsor of any pregnancy while receiving or within 6 months of the dose of quizartinib or dabigatran etexilate in a female subject or a male subject's female partner using the Exposure In Utero (EIU) Reporting Form.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy as this information is important for drug safety and public health concerns.

The investigator should make every effort to follow the female subject or partner of a male subject (upon obtaining written consent from partner) until completion of the pregnancy and record the complete pregnancy outcome information, including normal delivery or induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. For reports of pregnancy in the female partner of a male subject, the EIU Reporting Form (or SAE form if associated with an adverse outcome) should be completed with the subject's ID number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

8.6.2.10. Pregnancy Testing

Women of childbearing potential will have a serum pregnancy test conducted at Screening and a urine pregnancy test at Day -1 and Day 12 (early termination [ET]/EOS).

For women of childbearing potential (as defined in Section 5.2), document the results of the negative serum pregnancy tests at Screening. For eligibility, a serum pregnancy test must be performed with the results available prior to enrollment.

Women who are postmenopausal will have an FSH test conducted at Screening.

8.6.3. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as detailed in the SoEs in Section 1.3.

The clinical laboratory tests will include hematology, coagulation, blood chemistry, and urinalysis. Subjects will have to fast (except water) for at least 10 hours before having blood drawn for these lab tests. Refer to Section 10.2 for the complete list of laboratory parameters.

Abnormal laboratory values occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically relevant. New or worsened clinically relevant laboratory abnormalities should be recorded as AEs.

Urine test for drugs of abuse (illegal and/or prescription), including tobacco and alcohol will be tested during Screening and Day-1. HBsAg/ HCV/HIV will be tested during Screening.

8.6.4. Physical Examinations

Physical examination will be performed as detailed in the SoE in Section 1.3.

A complete physical examination should include a height (at Screening only), weight (at Screening, Day -1, and Day 12 [ET/EOS]), and calculation of BMI (at Screening only), and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations can be performed at the discretion of the investigator. Changes from baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs.

8.6.5. Vital Signs

Vital signs will be performed as detailed in the SoE in Section 1.3.

Allowable time windows for vital sign assessments are provided in Section 10.7.

Vital signs will include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, and temperature. Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes, prior to laboratory draws, and at the same timepoints as ECGs.

8.6.6. Electrocardiograms

Electrocardiograms will be performed as detailed in the SoE in Section 1.3.

Allowable time windows for ECGs are provided in Section 10.7.

Triplicate 12 lead-ECGs (approximately 2 minutes apart) will be performed at least 5 minutes before any blood collection and will be recorded for every subject. The ECG will be measured after the subject has rested in a supine position for at least 5 minutes. 12-lead ECG should be recorded in triplicate with the clinical site's equipment (3 separate ECGs at least 2 minutes apart; the average of the 3 QTcF determinations used to determine safety parameters). ECGs should be obtained once, in triplicate, at Screening, on Day -1, and on Day 12 (ET/EOS). On Day 1 of Period 1, triplicate ECGs will be recorded within 1 hour prior to dabigatran etexilate administration and 2, and 6 hours after dabigatran etexilate administration. On Day 5 of Period 2, triplicate ECGs should be recorded within 1 hour prior to quizartinib administration and 2, 4, and 8 hours after quizartinib administration.

Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Whether or not the measurement is performed, the date the ECG is to be performed and results will be recorded.

8.7. Pharmacogenomic (Inherited Genetic) Analysis

A single blood sample for pharmacogenomic (PGx) analysis will be collected predose from each randomized subject. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Laboratory Specifications Document as detailed in Section 10.6.

Genetic analyses will not be performed on blood samples collected for PK or safety assessments. Subject confidentiality will be maintained.

DNA samples will be stored, as outlined in Section 8.7.2 for performing possible PGx analysis in the future; otherwise all remaining DNA samples will be destroyed.

8.7.1. Banking of Specimens for Inherited Genetic Analysis

Procedures for the long-term preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject that consented are described in Section 10.6.

The banked samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of quizartinib. Additionally, samples may be analyzed for genes involved in quizartinib related signaling pathways, or to examine diseases or physiologic processes related to quizartinib. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

8.7.2. Storage and Disposal of Specimens

Banked DNA samples will be stored for a maximum of 15 years after the finalization of the clinical study report for this protocol. These specimens will be kept for pharmacogenetic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK) to quizartinib, or in case serious adverse drug reactions are noted in a clinical study and pharmacogenetic analysis is to be conducted for investigation into the cause.

During the storage period, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if analysis has been completed before the subject withdraws consent.

8.7.3. Disclosure of the Results of Future Pharmacogenetic Analysis

Because the nature and value of future pharmacogenetic analysis cannot be known at this time, any results obtained from research involving pharmacogenetic samples will not be disclosed to the subject or investigators now or in the future.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

This is not a hypothesis testing study.

9.2. Sample Size Determination

The number of subjects was not based on statistical power considerations; however, a target sample size of 20 was calculated to provide 90% confidence that the estimated ratios (with and without quizartinib) of dabigatran etexilate geometric mean Cmax and AUC values would be within 10% of true population values. The calculation assumed that AUC and Cmax were log-normally distributed with a within subject coefficient of variation (CV%) of <30% for AUC and Cmax.

9.3. Exposure and Compliance

As the dose administration is under the control of the study sites, compliance to study medication will not be an issue. Study drug administration will be summarized by subject, treatment, and time of dosing.

9.4. Population for Analysis Sets

9.4.1. Pharmacokinetic Population

The PK analysis will be performed using the PK Population defined as all evaluable subjects who received at least 1 dose of study drug (quizartinib or dabigatran) and has a measurable concentration.

9.4.2. Safety Population

The safety analysis will be performed using the Safety Population defined as all subjects who receive at least 1 dose of dabigatran etexilate or quizartinib.

9.5. Statistical Analysis

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Safety Analysis

9.5.1.1. Adverse Events

Treatment-emergent adverse events are defined as new AEs that occur after the first dose of study drug or as AEs that were present prior to first dose of study drug but which worsened in severity after the start of study drug. AEs collected 30 days after the last dose of study drug will not be considered TEAEs unless they are treatment-related. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE will be assigned to the study

day in which it started, even if it resolved on a subsequent day. The incidence of TEAEs will be summarized by treatment group. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group.

Treatment-emergent adverse events will be further summarized by common terminology criteria for adverse events (CTCAE) grade and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and related treatment-emergent SAEs will be tabulated, treatment-emergent AESIs, and TEAEs leading to discontinuation of study drug.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study drug will be provided. Deaths, SAEs, AESIs, and AEs associated with study drug discontinuation will be listed.

9.5.1.2. Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment group, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at Day 12.

Abnormal clinical laboratory results will be graded according to National Cancer Institute - common terminology criteria for adverse events (NCI-CTCAE) Version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by treatment group the two-way frequency tabulation for baseline and the worst post-treatment value according to the CTCAE grade, will be provided for clinical laboratory tests. A listing of abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be generated.

9.5.1.3. Electrocardiograms

Results of triplicate ECGs and change from baseline will be summarized with descriptive statistics at each time point. The baseline value is defined as the last non-missing value before the initial administration of study drug. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc $\leq$450 ms, >450 to $\leq$480 ms, >480 ms to $\leq$500 ms, and >500 ms).

A listing of ECG data will be generated.

9.5.1.4. Vital Signs

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. A listing of vital sign data will be generated.

9.5.1.5. Other

Listings of all other safety endpoints (eg, physical examination findings) will be generated.

9.5.2. Pharmacokinetics Analysis

Pharmacokinetic analysis and statistical analysis of PK endpoints will be conducted in accordance with the protocol, SAP, and the Daiichi Sankyo, Inc. Non-Compartmental Analysis Guidelines.

9.5.2.1. Pharmacokinetic Parameters

Pharmacokinetic and statistical analysis will be performed using appropriate software; eg, Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.).

The following PK parameters will be calculated for dabigatran, quizartinib and AC886, as applicable.

Cmax	Maximum concentration, determined directly from individual concentration-time data
Tmax	Time to reach maximum concentration
t1/2	The observed terminal half-life (for dabigatran only)
AUC0-74 (truncated AUC)	Area under the concentration-time curve from time 0 to 74 hours (for quizartinib and AC886 only)
AUClast	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule (for dabigatran only)
AUCinf	Area under the concentration-time curve from time-zero extrapolated to infinity (for dabigatran only)

9.5.2.2. Statistical Analysis of Pharmacokinetic Endpoints

The PK parameters for dabigatran and for quizartinib and AC886 will be determined using non-compartmental modeling and summarized with descriptive statistics.

To assess the effect of quizartinib on the PK of dabigatran, geometric least square mean (Geo LSM) ratios of Cmax, AUClast, and AUCinf from treatments with and without quizartinib, and their 90% confidence intervals (CIs) will be determined. Each comparison will also be made by performing an analysis of covariance (ANCOVA) on the logarithm-transformed Cmax, AUClast, and AUCinf.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the IB, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the independent IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB.

The investigator should notify the IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports in accordance with local procedures.

The Sponsor will appoint an investigator. Among other possible duties, the investigator will be responsible for reviewing the Final Clinical Study Report and testifying to the accuracy of the description of the study conduct. Because the investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those investigators who have enrolled and treated at least one subject. However, where an investigator has special knowledge of the field or of the study, the investigator can be chosen prior to enrollment of the first subject. In all cases, the investigator must be chosen prior to locking the data base.

10.1.2. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Other applicable local regulations.

In addition, the investigator will inform the Sponsor in writing within 24 hours of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

10.1.3. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study,

IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB. The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

10.1.4. Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The ICF and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed ICF should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

Suggested model text for the ICF for the study and any applicable subparts (PK, PD, etc) is provided in the Sponsor's ICF template for the investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study sites in the United States (US), an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

10.1.5. Subject Confidentiality

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should be identified by unique subject identification (SID) as designated by the Sponsor. Documents that are not for submission to the Sponsor or the contract research organization (CRO) (eg, signed ICF) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the independent IRB direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

10.1.6. Data Integrity and Quality Assurance

10.1.6.1. Monitoring and Inspections

The Sponsor monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings.

In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

10.1.6.2. Data Collection

An eCRF must be completed for each subject. Screen failure information will be collected at the clinical site in a log. All data collected during the study will be recorded in the individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the investigator via the electronic data capture (EDC) system's electronic signature. This signature will indicate that the investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

10.1.6.3. Data Management

Each subject will be identified in the database by a unique SID.

To ensure the quality of clinical data across all subjects and study sites, a CRO Clinical and Data Management review will be performed on subject data according to specifications developed by the Sponsor. Data will be vetted both electronically by programmed data rules within the application and manually. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

All AEs will be coded using MedDRA. Serious adverse events in the clinical database will be reconciled with the safety database.

10.1.6.4. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to obtain informed consent and make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date and outcome of the screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential SID code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Electronic CRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, the study eCRF may be used as source documents.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed ICFs, investigator's Agreement, clinical supplies receipts, distribution, and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (site specific Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by local laws or regulations or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to provide further instruction.

10.1.6.5. Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (site specific Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable laws or regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/Institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or

move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

10.1.7. Finances

Prior to starting the study, the investigator and/or Institution will sign a clinical study agreement with CRO. This agreement will include the financial information agreed upon by the parties.

10.1.8. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.9. Publication and Public Disclosure Policy

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, European Union (EU), and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

10.1.10. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

The Sponsor must be notified in writing of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) within 24 hours and in accordance with the clinical study agreement between the parties.

The investigator, or person designated by the investigator, should document, and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study drug, and had at least one administration of study drug, data should be collected for safety purposes.

If applicable, the investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

10.1.11. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

Study termination may also be requested by (a) competent authority(ies).

10.1.12. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative form the Sponsor.

For product complaints, refer to the Pharmacy Manual for instructions and details.

10.2. Appendix 2: Central and/or Local Laboratory

The clinical laboratory tests listed in Table 10.1 are to be performed in this study.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry	albumin albumin globulin (A/G) ratio alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bicarbonate/CO2 bilirubin (total) bilirubin (direct) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine cholesterol (total) creatine	creatine phosphokinase gamma-glutamyl transaminase (GGT) glucose ([non-fasting/fasting]) lactate dehydrogenase lipase lipoprotein, high density (HDL) lipoprotein, low density (LDL) magnesium (Mg) phosphorus potassium (K) protein (total) sodium (Na) triglycerides uric acid
Hematology	hemoglobin hematocrit platelet count red blood cell (RBC) count white blood cell (WBC) count mean corpuscular hemoglobin mean corpuscular hemoglobin concentration mean corpuscular volume	differential WBC count: basophils eosinophils lymphocytes monocytes neutrophils
Coagulation	activated partial thromboplastin time (aPTT)/prothrombin time (PT)/international normalized ratio (INR)	
Urinalysis (abbreviated)	bilirubin glucose ketone bodies occult blood pH protein	urobilinogen sediments: casts RBC WBC

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated CrCl (mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds) [2]:

Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in y)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in y)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in y)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in y)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113} \times 0.85$$

10.3.2. Corrected Calcium Formula for Eligibility

To correct calcium for serum albumin in case of hypoalbuminemia for eligibility, as referenced in inclusion criterion Section 5.1, please use one of the following formulas[3]:

In mg/dL:

Corrected Calcium [mg/dL] = (0.8 × (Normal Albumin - Albumin) + Calcium

In mmol/L:

Corrected Calcium [mmol/L] = (0.02 × (Normal Albumin - Albumin) + Calcium

10.3.3. Highly Effective Contraception

Methods considered to be highly effective contraception include[4]:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence

10.3.4. CYP3A4 Inhibitors and Inducers

Table 10.2 lists the generic names of strong, moderate, and weak CYP3A4 inhibitors.

Table 10.2: CYP3A4 Inhibitors

Inhibitor Type	Generic Drug Name	Allowance
Strong	boceprevir cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice indinavir and ritonavir itraconazole ketoconazole, lopinavir, and ritonavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir telithromycin troleandomycin voriconazole	Use is prohibited
Moderate	aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil	Use is prohibited
Weak	chlorzoxazone cilostazol cimetidine clotrimazolefosaprepitant istradefylline ivacaftor lomitapide	Use is prohibited

Inhibitor Type	Generic Drug Name	Allowance
	ranitidine ranolazine ticagrelor	

Source: https://www fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

Table 10.3 lists the generic names of strong, moderate, and weak CYP3A4 inducers.

Table 10.3: CYP3A4 Inducers

Inducer_Type	Generic Drug Name	Allowance
Strong	apalutamide carbamazepine enzalutamide mitotane phenytoin rifampin St. John's wort	Use is prohibited
Moderate	bosentan efavirenz etravirine phenobarbital primidone	Use is prohibited
Weak	armodafinil modafinil rufinamide	Use is prohibited

Source: https://www fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3

10.4. Appendix 4: General Information - Adverse Events

10.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

10.4.1.1. Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected DDI.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

10.4.1.2. Events NOT Meeting the AE Definition

- Any clinically relevant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.4.2. Serious Adverse Event

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

- Results in death

- Is life-threatening
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at 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 event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - 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 with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is an important medical event
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3. Grade Assessment

The severity of AEs will be graded using the latest NCI-CTCAE (Version 5.0). For each episode, the highest severity grade attained should be reported.

The NCI-CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4

or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI-CTCAE guidelines should be followed closely.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

10.4.4. Difference between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.4.5. Causality Assessment

The investigator should assess causal relationship between an AE and the study drug based on his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study (or its chemical group) or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.4.6. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Drug Interrupted: The study drug was temporarily stopped.
- Unknown: Subject is lost to follow-up

10.4.7. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the AE.

10.4.8. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no sequelae observed.
- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE
- Unknown

d) Expected delivery date and time (if available)
e) Number of samples included in the shipment
f) Shipment tracking or airway bill number
g) Email address(s) for shipment receipt acknowledgments

The bioanalytical laboratory for PK plasma samples will be:

PPD

BASi

2701 Kent Avenue

West Lafayette, IN 47908

PPD

PPD

The shipping address for PK plasma samples will be:

BASi

2701 Kent Avenue

West Lafayette, IN 47908

ATTN: Sample Management

d) Expected delivery date and time (if available)
e) Number of samples included in the shipment
f) Shipment tracking or airway bill number
g) Email address(s) for shipment receipt acknowledgments

The bioanalytical laboratory for PK plasma samples will be:

Orlando Bravo
BASi
2701 Kent Avenue
West Lafayette, IN 47908
Phone: (765) 497-8351
Email: obravo@basinc.com

The shipping address for PK plasma samples will be:

BASi
2701 Kent Avenue
West Lafayette, IN 47908
ATTN: Sample Management

10.6. Appendix 6: Pharmacogenomic Blood Samples Collection, Processing, Storage, and Shipment

As part of this study, a genotyping blood sample (1 × 3 mL) will be taken from each subject on Study Day 1. This sample will be stored for possible future PGx and/or PGx analysis. At Screening, all potential subjects should be presented with the standard ICF, which will include details of these procedures.

In the future, the stored sample may be used for genetic and PGx tests related to study drug exposure or response and to explore disease pathophysiology if warranted. Specific candidate genes and the entire genome may be examined. This may provide information on how individuals react to the study medication and may facilitate improvements in the understanding of differences among individuals with respect to the way the study medication is metabolized. It may also help in the development of new drugs or improvement of existing drugs. The results of the genetic analysis will not be provided to subjects or the investigator, nor can the results of this analysis be requested at a later date. A subject may not request withdrawal of the PGx blood sample after it has been obtained. Any information obtained from the PGx research will be the property of the Sponsor. The PGx samples will be stored frozen for up to 15 years, at which time they will be destroyed. During this time, the DNA sample will not be immortalized or sold to anyone.

Pharmacogenomic blood samples will be processed as described below.

	Processing Instructions
1	PGx blood samples are collected as whole blood in a 3 mL Becton-Dickinson (BD) Vacutainer® lavender top K2-EDTA tube with Hemogard™ closure. 
2	**Do not centrifuge**
3	Transfer whole blood to a 3 mL cryovial that is suitable for longterm storage of whole blood at ultra-low temperatures for storage and shipment.
4	Freeze immediately.
5	Store samples at -80°C or at -20 °C (only in non-cycling freezer) if a -80°C freezer is not available.

A. Labeling of storage tubes

Labels should be secured to each storage tube.

Sample label should include:

a) Designated set number

b) Subject number

c) Study number
d) Protocol number, if applicable
e) Barcode, if applicable
f) Time points
g) Aliquot number

B. Shipment

PGx blood samples will be shipped on dry ice.

Please copy Rebecca Indibi on shipment notification from the central laboratory to provide necessary documents to Fisher Clinical Services in advance of each shipment.

PPD

Associate Director, Clinical Sample Management

Daiichi Sankyo, Inc.

211 Mt. Airy Road

Basking Ridge, NJ 07920

PPD

The bioanalytical laboratory for PGx blood samples will be:

Thermo Fisher Scientific

14665 Rothgeb Drive

Rockville, MD 20850

The shipping address for PGx blood samples will be:

PPD

Thermo Fisher Scientific

14665 Rothgeb Drive

Rockville, MD 20850

PPD

www.fisherbioservices.com

10.7. Appendix 7: Allowable Time Windows for Pharmacokinetic Blood Samples, and Vital Sign and Electrocardiogram Assessments

Table 10.4: Acceptable Time Windows

Procedures (in order of collection)	Allowable Time Window	
	Predose	Postdose
ECG (predose and 2 and 6 hours post-dabigatran dose).	No more than **30** minutes before dose; inclusive of at least 5 minutes of quiet rest in the supine position postdose with 5 additional minutes allowed	No more than **6** minutes after dose; inclusive of at least 5 minutes of quiet rest in the supine position postdose with 1 additional minute allowed
(predose and 2, 4, and 8 hours post-quizartinib dose)	Approximately 2 minutes between triplicate ECGs with 1 additional minute allowed between each of the triplicate ECGs	Approximately 2 minutes between triplicate ECGs with 1 additional minute allowed between each of the triplicate ECGs
Vital signs (predose, 2, 4, and 8 hours postdose)	No more than **15** minutes before dose; inclusive of at least 5 minutes of supine rest with 5 additional minutes allowed	No more than **6** minutes after dose; inclusive of at least 5 minutes of supine rest with 1 additional minute allowed
PK sample collection (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dabigatran dose) (predose and 1, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 26, 38, 50, 62, and 74 hours post-quizartinib dose)	± 60 minutes	±2 minutes (0.5 and 1 hour postdose)
		No more than **15** minutes after dose inclusive of the windows for ECGs and vital signs (1.5, 2, 2.5, 3, 3.5, 4, 5 hours postdose)
		±15 minutes (6, 8, 10, 12, 14 and 24 hours postdose)
		±30 minutes (26 through 72/74 hours postdose)

ECG = electrocardiogram; PK = pharmacokinetics.
Note: ECG will be performed prior to PK.

11. REFERENCES

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4. Heads of Medicines Agencies. Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 2014. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

12. LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
ART	assisted reproductive technology
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CFR	Code of Federal Regulations
Cmax	maximum concentration
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DDI	drug-drug interaction
DSI	Daiichi-Sankyo, Inc.
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
HBsAg	hepatitis b virus surface antigen

Abbreviation	Definition
HCV	hepatitis C virus
HI	hepatic impairment
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
IMP	investigational medicinal product
INN	international non-proprietary name
INR	international normalized ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute - common terminology criteria for adverse events
OTC	over-the-counter
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SID	subject identification
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum plasma concentration
t1/2	half-life
ULN	upper limit of normal
US	United States