CLINICAL STUDY PROTOCOL

An Open-label, Randomized, Parallel-group, Drug Interaction Study to Evaluate the Effect of a CYP3A Moderate Inducer Efavirenz on the Pharmacokinetics of Quizartinib in Healthy Subjects

Effect of a Moderate CYP3A Inducer Efavirenz on Quizartinib Pharmacokinetics

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INVESTIGATOR AGREEMENT

An Open-label, Randomized, Parallel-group, Drug Interaction Study to Evaluate the Effect of a CYP3A Moderate Inducer Efavirenz on the Pharmacokinetics of Quizartinib in Healthy Subjects

Sponsor Approval:

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

PPD	DocuSigned by: PPD Signing Reason: I approve this document Signing Time: 05-Aug-2020 | 16:01:50 EDT D12BDA0D56B34176AD15179DB7B282ED
Print Name	**Signature**
PPD	05-Aug-2020 | 16:01:53 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	DocuSigned by: PPD Signing Reason: I approve this document Signing Time: 06-Aug-2020 | 09:48:57 CDT FA8DB484FD847B5A4A33071357CA7F7
Print Name	**Signature**
PPD	06-Aug-2020 | 09:49:01 CDT
Title	**Date (DD MMM YYYY)**

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1.1. Protocol Synopsis

Protocol Title
An Open-label, Randomized, Parallel-group, Drug Interaction Study to Evaluate the Effect of a CYP3A Moderate Inducer Efavirenz on the Pharmacokinetics of Quizartinib in Healthy Subjects
Protocol Short Title
Effect of a Moderate CYP3A Inducer Efavirenz on Quizartinib Pharmacokinetics
Protocol Number
AC220-A-U106
Sponsor/Collaborators
Daiichi Sankyo, Inc.
Registry Identification(s)
• NCT04459598
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 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 that have outcome measures.

Objectives	Outcome Measure	Category
Primary		
To determine the effect of efavirenz on the plasma pharmacokinetics (PK) of quizartinib and AC886 in healthy subjects	Plasma PK parameters (Cmax AUClast, AUCinf) for quizartinib and its active metabolite (AC886); additionally Tmax, t1/2, metabolite-to-parent ratio (MPR) AUClast, and MPR AUCinf for quizartinib and its active metabolite (AC886), and CL/F and Vz/F for quizartinib only	Pharmacokinetics
Secondary		
To assess the safety and tolerability of quizartinib in healthy subjects when administered alone and when co-administered with efavirenz	Treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiograms (ECG), clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis), and physical examinations	Safety

Study Design

This is an open-label, randomized, parallel-group, Phase 1 study in 32 healthy subjects to assess the effect of the moderate CYP3A inducer efavirenz on the PK of quizartinib and its metabolite AC886. After a 21-day Screening Period, eligible subjects will be enrolled and will check-in to the clinical research unit (CRU) on Day -1. Subjects will be randomized in a 1:1 ratio on Day 1 to either Treatment Group A to receive a 600-mg efavirenz tablet once daily for 35 days and a single dose of 60-mg quizartinib (2 × 30 mg) on Day 15 or to Treatment Group B to receive a single dose of 60-mg quizartinib on Day 1. Collection of blood samples for PK determinations and safety assessments will be collected predose and at selected timepoints postdose in both treatment groups.

Treatment Group A: Subjects will begin a regimen of 600-mg efavirenz tablet once daily on Day 1 and will continue the regimen through Day 35. Efavirenz will be taken before bedtime on an empty stomach (no food for at least 2 hours before and after dosing). On Day 15, subjects will receive a single dose of 60-mg quizartinib (2 × 30 mg) with 240 mL of water after 10 hours of fasting. Quizartinib will be taken in the morning followed by an additional 4 hours of fasting. Pharmacokinetic blood samples will be collected from Day 15 through Day 36. Subjects will be discharged from the CRU and from the study at end-of-study (EOS) on Day 36 after study procedures are completed. Safety assessments will be conducted from Day 1 through Day 36.

Treatment Group B: On Day 1, subjects will be given a single dose of 60-mg quizartinib (2 × 30 mg) with 240 mL of water after 10 hours of fasting. Quizartinib will be taken in the morning followed by an additional 4 hours of fasting. Pharmacokinetic blood samples will be collected from Day 1 through Day 22. Subjects will be discharged from the CRU and from the study at EOS on Day 22 after study procedures are completed. Safety assessments will be conducted from Day 1 through Day 22.

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 this 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.

The duration of the study for each subject in Treatment Group A is up to 58 days and for each subject in Treatment Group B is up to 44 days.

The anticipated total duration of the study is approximately 2 months.

Key Eligibility Criteria

Key Inclusion Criteria:

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

- 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.
- Has vital signs (measured after subject has been supine for at least 5 minutes) at Screening within the following ranges: heart rate: 50–100 bpm; systolic blood pressure (BP): 90–145 mmHg; diastolic BP: 50-95 mmHg.
- Liver function test results (ALT, AST, and total bilirubin) must be equal to or below the upper limit of normal. Hemoglobin levels must be at least 11.5 g/dL for female subjects and at least 12.5 g/dL for male subjects.
- 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.
- 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.

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:

- History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition, including laboratory abnormality, that in the opinion of the Investigator, would jeopardize the safety of the subject, obtaining informed consent, compliance to the study procedures, or the validity of the study results.
- History of a clinically significant illness, in the opinion of the Investigator, within 4 weeks prior to administration of quizartinib.
- History, or presence in the average of triplicate ECGs at Screening and Day -1, of any of the following cardiac conduction abnormalities:
  - QTcF > 450 milliseconds (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)
- Women who are pregnant or breastfeeding
- Laboratory results (serum chemistry, hematology, and urinalysis) outside the normal range, if considered clinically significant by the investigator. Estimated glomerular filtration rate (eGFR) <90 mL/min (calculated using Cockcroft-Gault Equation) at Screening.
- Use of drugs with a risk of QT interval prolongation or Torsades de Pointes (TdP) 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

Test group, product, dosage, and mode of administration:

Treatment Group A (efavirenz + quizartinib)
Efavirenz oral tablet, 600 mg
Dose = 600 mg (1 × 600 mg) once daily on Days 1 through 35
Quizartinib oral tablet, 30 mg
Dose = 60 mg (2 × 30 mg) single dose on Day 15

Reference group, product, dosage, and mode of administration:

Treatment Group B (quizartinib alone)
Quizartinib oral tablet, 30 mg
Dose = 60 mg (2 × 30 mg) single dose on Day 1

Active Ingredient

Quizartinib hydrochloride

Planned Sample Size

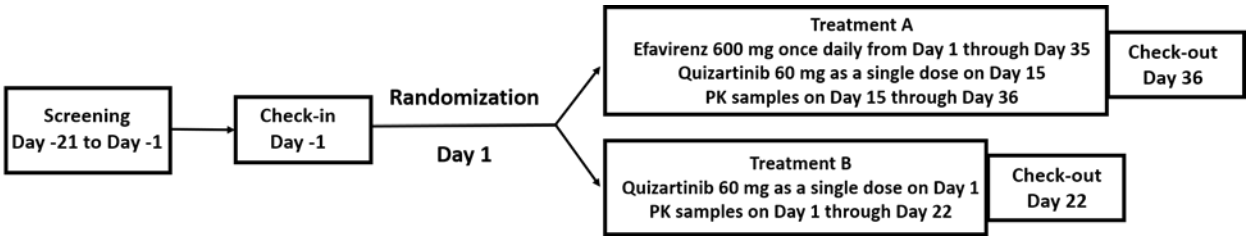
This study will comprise 32 healthy subjects randomized in a 1:1 ratio to 1 of 2 treatment groups.

Treatment Group A (test treatment) will enroll 16 healthy subjects.

Treatment Group B (reference treatment) will enroll 16 healthy subjects.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



PK = pharmacokinetic

1.3. Schedule of Events

Table 1.1: Treatment Group A

Study Period	**Screening[a]**	**Check-in**	**Treatment Period**										**EOS/ET[b]**
Study Day	**Day -21 to Day -1**	**Day -1**	**Days 1 - 14**	**Day 15**		**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Days 20 - 35**			**Day 36**
PK Samples Postdose (hours)				**Predose**	**<24**	**24**	**48**	**72**	**96**	**144 - 432**			**504**
Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographic Information	X												
Medical/Surgical History	X	X											
Prior/Concomitant Medications	<----------continuous---------->												
Complete Physical Examinations[c]	X	X	X										X
Body Weight and BMI[d]	X	X											X
Height	X												
Urine Drugs of Abuse and Alcohol Screen	X	X											
Virology (HBsAg/HIV/HAV/HCV)	X												
Serum Pregnancy Test (WOCBP)[e]	X	X											
FSH[f]	X												
Hematology, Serum Chemistry[g]	X	X	X	X					X		X		X
Coagulation (PT, INR)	X	X		X					X				X
Urinalysis	X	X							X				X
12-lead ECGs[h]	X	X		X	X								X
Vital Signs (BP, pulse, respiratory rate, oral temperature)[i]	X	X		X	X								X
Efavirenz Administration[j]			X	X	X	X	X	X	X	X	X	X	
Quizartinib Administration[k]				X									
PK Blood Samples[l]				X	X	X	X	X	X	X	X	X	X
PGx Sample				X									

Study Period	**Screening**[a]	**Check-in**	**Treatment Period**										**EOS/ET**[b]
Study Day	**Day -21 to Day -1**	**Day -1**	**Days 1 - 14**	**Day 15**		**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Days 20 - 35**			**Day 36**
PK Samples Postdose (hours)				**Predose**	**<24**	**24**	**48**	**72**	**96**	**144 - 432**			**504**
Procedures													
AE Monitoring	X	X	<----------continuous---------->										
Check-in		X											
Confinement		<----------continuous---------->											
Discharge													X

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOS = end-of-study; ET = early termination; FSH = follicle-stimulating hormone; HAV = hepatitis A virus; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PGx = pharmacogenomic; PK = pharmacokinetic; PT = prothrombin time; WOCBP = women of childbearing potential

a To be conducted within 21 days prior to dosing

b Following final blood collections; same procedures to be performed at ET as at EOS.

c A full physical examination that includes an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems will be performed at Screening, and on Day -1, Day 14, and EOS.

d BMI at Screening only

e Female subjects (WOCBP only)

f Naturally postmenopausal female subjects only

g Blood samples for hematology and serum chemistry will be collected after a 10-hour fast at Screening, and on Day -1, Day 7, predose (quizartinib) on Day 15, and on Day 19, Day 27, and EOS.

h Triplicate ECG (approximately 2 minutes apart) and after at least 5 minutes of quiet rest in the supine position. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken at least 5 minutes prior to the blood collection and at predose, 2, 4, and 8 hours after quizartinib administration.

i Vital signs will be taken after at least a 5-minute supine rest; vital signs should be taken at all ECG timepoints.

j Efavirenz will be dosed as 600 mg once daily from Day 1 through Day 35. Efavirenz will be taken before bedtime on an empty stomach (no food for at least 2 hours before and after dosing).

k A single dose of 60-mg quizartinib (2 × 30 mg) will be administered following an overnight fast of 10 h on Day 15. Water consumption will be restricted from 1 hour predose to 2 hours postdose, except for the 240 mL of water that is to be administered with quizartinib. Subjects will continue to fast for 4 hours postdose.

l Day 15 through 36 (relative to quizartinib) PK samples for quizartinib will be collected at predose, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, 216, 288, 360, 432, and 504 hours post-quizartinib dose. 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.

Table 1.2: Treatment Group B

Study Periods	**Screening**[a]	**Check-in**	**Treatment Period**									**EOS/ET**[b]
Study Day	**Day -21 to Day -1**	**Day -1**	**Day 1**		**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Days 6 - 21**			**Day 22**
PK Sampling Postdose (hours)			**Pre-dose**	**<24**	**24**	**48**	**72**	**96**	**144 - 432**			**504**
Procedures												
Informed Consent	X											
Admission		X										
Inclusion/Exclusion Criteria	X	X										
Demographic Information	X											
Medical/Surgical History	X	X										
Prior/Concomitant Medications	<----------continuous---------->											
Complete Physical Examinations[c]	X	X								X		X
Body Weight and BMI[d]	X	X										X
Height	X											
Urine Drugs of Abuse and Alcohol Screen	X	X										
Virology (HBsAg/HIV/HAV/HCV)	X											
Serum Pregnancy Test (WOCBP)[e]	X	X										
FSH[f]	X											
Hematology, Serum Chemistry[g]	X	X						X		X		X
Coagulation (PT, INR)	X	X	X					X				X
Urinalysis	X	X						X				X
12-lead ECGs[h]	X	X	X	X								X
Vital Signs (BP, pulse, respiratory rate, oral temperature)[i]	X	X	X	X								X
Quizartinib Administration[j]			X									
PK Blood Samples[k]			X	X	X	X	X	X	X	X	X	X
PGx Sample			X									
AE Monitoring	X	X	<----------continuous---------->									
Check-in		X										

Study Periods	**Screening**[a]	**Check-in**	**Treatment Period**									**EOS/ET**[b]
Study Day	**Day -21 to Day -1**	**Day -1**	**Day 1**		**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Days 6 - 21**			**Day 22**
PK Sampling Postdose (hours)			**Pre-dose**	**<24**	**24**	**48**	**72**	**96**	**144 - 432**			**504**
Procedures												
Confinement		<----------continuous---------->										
Discharge												X

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOS = end-of-study; ET = early termination; FSH = follicle-stimulating hormone; HAV = hepatitis A virus; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PGx = pharmacogenomic; PK = pharmacokinetic; PT = prothrombin time; WOCBP = women of childbearing potential

a To be conducted within 21 days prior to dosing

b Following final blood collections; same procedures to be performed at ET as at EOS

c A full physical examination that includes an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems will be performed at Screening, and on Day -1, Day 14, and EOS.

d BMI at Screening only

e Female subjects (WOCBP only)

f Naturally postmenopausal female subjects only

g Blood samples for hematology and serum chemistry will be collected after a 10-hour fast at Screening, and on Day -1, Day 5, Day 13, and EOS.

h Triplicate ECG (approximately 2 minutes apart) and after at least 5 minutes of quiet rest in the supine position. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken at least 5 minutes prior to the blood collection and at predose, 2, 4, and 8 hours after quizartinib administration.

i Vital signs will be taken after at least a 5-minute supine rest; vital signs should be taken at all ECG timepoints.

j A single dose of 60-mg quizartinib (2 × 30 mg) will be administered following an overnight fast of 10 h on Day 1. Water consumption will be restricted from 1 hour predose to 2 hours postdose, except for the 240 mL of water that is to be administered with quizartinib. Subjects will continue to fast for 4 hours postdose.

k Day 1 through 22 (relative to quizartinib) PK samples for quizartinib will be collected at predose, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, 216, 288, 360, 432, and 504 hours post-quizartinib dose. 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.

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 h (range: 2 h to 8 h) and 5 h (range: 4 h to 120 h) 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 h and 119 h, 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. Therefore, this study aims to evaluate the effect of a moderate CYP3A inducer, efavirenz, on quizartinib PK.

This is an open-label, randomized, parallel-group, drug interaction study to evaluate the effect of a moderate CYP3A moderate inducer efavirenz on the PK of quizartinib in healthy male and female subjects.

2.2. Study Rationale

In vitro reaction phenotyping using human liver microsomes and recombinant human CYP enzymes showed that quizartinib is metabolized primarily by CYP3A. Concomitant administration of strong (ketoconazole) and moderate (fluconazole) CYP3A inhibitors increased quizartinib area under the plasma concentration-time curve (AUC) by 94% and 20%, respectively. In a previously conducted drug-drug (DDI) interaction study, coadministration of multiple doses of the strong CYP3A inducer rifampin with a single quizartinib dose of 60 mg

resulted in approximately 70% decrease in quizartinib AUC. However, due to bioanalytical issues, the results were not quantitatively conclusive. Therefore, the current DDI study has been designed to investigate the effect of a moderate CYP3A inducer efavirenz on the PK of quizartinib and its major circulating metabolite AC886.

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 efavirenz or quizartinib is intended or expected.

In the 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 a single dose of quizartinib. Toxicities observed for quizartinib in healthy subjects (n = 307) following single dose administration were headache (21 [6.8%] subjects), upper respiratory tract infection (8 [2.6%] subjects), and diarrhea (6 [2.0%] subjects). QT prolongation and combined elevations of ALT >3 × ULN and TBil >2 × ULN are the two adverse events of special interest following quizartinib dosing. In approximately 3% of patients with AML in a Phase 3 clinical study with repeated daily dosing, the QTc interval was prolonged to 500 milliseconds or more.

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 QTcF interval greater than 500 ms, and 12.4% had an increase from baseline QTcF greater than 60 ms based on central review of 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 in which 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 relapsed/refractory 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 efavirenz and the most recent version of the Investigator's Brochure 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 determine the effect of efavirenz on the plasma PK of quizartinib and AC886 in healthy subjects.

The primary endpoints of this study are:

- Plasma PK parameters (Cmax AUClast, AUCinf) for quizartinib and its active metabolite (AC886); additionally Tmax, t1/2, metabolite-to-parent ratio (MPR) AUClast, and MPR AUCinf for quizartinib and its active metabolite (AC886), and CL/F and Vz/F for quizartinib only.

3.2. Secondary Objective /Endpoint

The secondary objective of this study is:

- To assess the safety and tolerability of quizartinib in healthy subjects when administered alone and when co-administered with efavirenz.

The secondary endpoints of this study are:

- Treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiograms (ECG), clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis), and physical examinations.

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 DDI studies.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, randomized, parallel-group, Phase 1 study in 32 healthy subjects to assess the effect of the moderate CYP3A inducer efavirenz on the PK of quizartinib and its major circulating metabolite AC886. After a 21-day Screening Period, eligible subjects will be enrolled and will check-in to the clinical research unit (CRU) on Day -1. Subjects will be randomized in a 1:1 ratio on Day 1 to either Treatment Group A to receive a 600-mg efavirenz tablet once daily for 35 days and a single dose of 60-mg quizartinib (2 × 30 mg) on Day 15 or to Treatment Group B to receive a single dose of quizartinib on Day 1. Collection of blood samples for PK determinations and safety assessments will be collected predose and at selected timepoints postdose in both treatment groups.

4.1.1. Design Overview

In this study, 32 eligible subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups; 16 subjects in Treatment Group A and 16 subjects in Treatment Group B.

At the beginning of the Screening Period, subjects will sign the informed consent form (ICF). During the 21-day Screening Period, subjects' eligibility will be confirmed. They will undergo medical history evaluation, physical examination, vital sign determination, ECGs, and clinical laboratory assessments.

During the Treatment Period, subjects will receive study drug in the assigned treatment group.

Treatment Group A: On Day 1, subjects will begin a regimen of 600-mg efavirenz tablet once daily and will continue the regimen through Day 35. Efavirenz will be taken before bedtime on an empty stomach (no food for at least 2 hours before and after dosing). On Day 15, subjects will receive a single dose of 60-mg quizartinib (2 × 30 mg), which will be administered with 240 mL of water after at least 10 hours of fasting. Quizartinib will be taken in the morning. Subjects will continue to fast for 4 hours postdose. Pharmacokinetic blood samples will be collected from Day 15 through Day 36. Subjects will be discharged from the CRU and from the study at end-of-study (EOS) on Day 36 after study procedures are completed. Safety assessments will be conducted from Day 1 through Day 36.

Treatment Group B: On Day 1, subjects will be given a single dose of 60-mg quizartinib (2 × 30 mg) with 240 mL of water after 10 hours of fasting. Quizartinib will be taken in the morning followed by an additional 4 hours of fasting. Pharmacokinetic blood samples will be collected from Day 1 through Day 22. Subjects will be discharged from the CRU and from the study at EOS on Day 22 after study procedures are completed. Safety assessments will be conducted from Day 1 through Day 22.

After study treatment is discontinued, subjects will be followed for 30 days for safety.

The subject population is described in Section 5. A flow diagram of study activities is presented in Figure 1.1.

4.1.2. End-of-Study

At the defined EOS in both treatment groups (Day 36 for Treatment Group A and Day 22 for Treatment Group B), subjects will have a final PK blood sample taken and safety assessments of AEs, laboratory tests, vital signs, ECGs, and physical examination conducted.

4.1.3. Dose Regimen

In Treatment Group A, subjects will be on a 35-day regimen of 600-mg efavirenz tablet once daily and will receive a single dose of 60-mg quizartinib (2 × 30 mg) on Day 15 of the efavirenz regimen. Efavirenz will be taken before bedtime on an empty stomach (no food for at least 2 hours before and after dosing). Quizartinib is to be administered with 240 mL of water in the morning after at least 10 hours of fasting. Subjects will continue to fast for 4 hours postdose.

In Treatment Group B, subjects will receive a single dose of 60-mg quizartinib (2 × 30 mg) on Day 1. Quizartinib is to be administered with 240 mL of water in the morning after at least 10 hours of fasting. Subjects will continue to fast for 4 hours postdose.

4.1.4. Duration

The duration of the study for each subject in Treatment Group A is up to 58 days and for each subject in Treatment Group B is up to 44 days.

The anticipated total duration of the study is approximately 2 months.

The study overall will be completed when the last datapoints for primary and secondary endpoints are collected and recorded.

4.2. Rationale for Study Design

In vitro reaction phenotyping using human liver microsomes and recombinant human CYP enzymes showed that quizartinib is metabolized primarily by CYP3A. Therefore, coadministration of quizartinib with CYP3A inducers may decrease its exposures. This DDI study has been designed to investigate the effect of a moderate CYP3A inducer efavirenz on the PK of quizartinib and AC886.

To assess the effect of efavirenz on quizartinib PK, the subjects in Treatment Group A will be given efavirenz at a clinical dose of 600 mg once daily for 35 days. On Day 15 of the efavirenz regimen, a single dose of 60-mg quizartinib (2 × 30 mg) will administered. Pharmacokinetic blood sampling will begin predose on Day 15 and will continue through Day 36 of the study. Efavirenz will be continued throughout the PK sample collection period of quizartinib. The lead-in 14 days of dosing with efavirenz 600 mg daily is necessary to maximize the induction of CYP3A while limiting the length of the study based on a survey of reported efavirenz DDI studies in the University of Washington DDI database and model-based analysis of efavirenz CYP3A induction time course.[1] A reference group, Treatment Group B, will be given a single dose of 60-mg quizartinib (2 × 30 mg) with PK sampling taken predose and through 22 days postdose. Safety assessments will be conducted on the basis of the known effects of efavirenz and quizartinib.

4.3. Justification for Dose

The quizartinib dose of 60 mg is the approved dose for relapse/refractory acute myeloid leukemia (AML) in Japan and the maximum maintenance therapeutic dose currently being investigated for AML first-line therapy in the QuANTUM-First study NCT02668653.[2] Therefore, the quizartinib dose of 60 mg was selected to assess the effect of efavirenz on quizartinib PK.

The efavirenz dose of 600 mg is the dose approved for use in the United States for the treatment of HIV, as well as in the published literature on DDI studies involving efavirenz.

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. Has vital signs (measured after subject has been supine for at least 5 minutes) at Screening within the following ranges: heart rate: 50–100 bpm; systolic blood pressure (BP): 90-145 mmHg; diastolic BP: 50-95 mmHg. Out-of-range vital signs may be repeated once.
8. Has liver function test results (ALT, AST, and total bilirubin) equal to or below the upper limit of normal. Hemoglobin levels must be at least11.5 g/dL for female subjects and at least 12.5 g/dL for male subjects.
9. Must agree to refrain from donation of blood from 56 days prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening.
10. Must be willing to refrain from consuming blood oranges, grapefruit, grapefruit juice, pomegranates, pomegranate juice, Seville (bitter) oranges, and star fruit from 10 days before Day -1 until EOS.
11. Is willing and able to remain in the study unit for the entire duration of the confinement period.

5.2. Exclusion Criteria

Subjects meeting any exclusion criteria for this study will be excluded from this study.

Medical History

1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition, including laboratory abnormality, that in the opinion of the Investigator, would jeopardize the safety of the subject, obtaining informed consent, compliance to the study procedures, or the validity of the study results.
2. History of a clinically significant illness, in the opinion of the Investigator, within 4 weeks prior to administration of quizartinib.
3. Bradycardia of less than 50 beats per minute.
4. History, or presence in the average of triplicate ECGs at Screening and Day -1, of any of the following cardiac conduction abnormalities:
    - QTcF > 450 milliseconds (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)
5. Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome).
6. Presence or history of clinically severe adverse reaction to any drug.
7. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (with the exception of appendectomy, hernia repair, and/or cholecystectomy).
8. 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.
9. History of moderate to heavy alcohol use defined as consumption of more than 28 units of alcohol per week for males or 14 units of alcohol per week for females, where 1 unit of alcohol equals one-half pint of beer, 4 ounces (oz) of wine, or 1 oz of spirits, or significant history of alcoholism or drug/chemical abuse within the last 2 years.
10. Loss of more than 450 mL blood during the 3 months before the trial (e.g., as a blood donor).

Medication Use and Lifestyle

11. 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).
12. Use of any drugs or substances known to be inhibitors or inducers of CYP3A4/5 within 28 days from the first dose or 5 half-lives, if known, of the drugs or substances, whichever is greater, prior to quizartinib administration and during the study.

13. Concomitant use of medications known to affect the elimination of serum creatinine (e.g., trimethoprim or cimetidine) and inhibitors of renal tubular secretion (e.g., probenecid) within 14 days or 5 half-lives, if known, of the drugs, whichever is greater, prior to quizartinib administration.
14. Use of any prescribed or over-the-counter (OTC) systemic, herbal (including St John's wort), or topical medication within 14 days of quizartinib administration, or any expectation of requiring use of such medication while participating in the study is prohibited.

    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.
15. Start of any new medication or any changes to a current dosage within 14 days prior to quizartinib administration excluding approved oral contraceptives.
16. Consumption of alcohol- and caffeine-containing beverages within 72 hours prior to Check-in and during confinement.
17. Has been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
18. Engagement in strenuous exercise from 48 hours before the first dose of study medication until the EOS.

Laboratory Tests

19. Is a female with a positive pregnancy test result or is lactating.
20. Laboratory results (serum chemistry, hematology, and urinalysis) outside the normal range, if considered clinically significant by the Investigator. Estimated glomerular filtration rate (eGFR) <90 mL/min (calculated using the Cockcroft-Gault Equation equation) at Screening.
21. Has a positive serology for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), hepatitis A virus (HAV) immunoglobulin M (IgM), or human immunodeficiency virus (HIV).
22. Has a positive urine screen for drugs of abuse or for ethanol at Screening or at Check-in on Day -1.
23. Current enrollment in or have not yet completed receiving an investigational device or product (at least 30 days or 5 elimination half-lives, whichever is longer) within 30 days of the dose of quizartinib.

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 Day 36 for Treatment Group A and Day 22 for Treatment Group B. 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 intrauterine device (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 TREATMENT(S)

6.1. Study Drug(s) Description

Table 6.1: Study Drug Dosing Information

Study Drug Name	Quizartinib	Efavirenz
Dosage Formulation	30-mg tablet [a]	600-mg tablet
Dosage Level(s)	60 mg	600 mg
Route of Administration	Oral	Oral
Dosing	Single dose	Once daily
Duration	Once	Once daily for 35 doses
Packaging	High-density polyethylene (HDPE) bottles of 30 tablets Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations	Bottles of 30 tablets
Labeling	Bottles will be labeled as required per local and regulatory requirements	Bottles will be labeled as required per local and regulatory requirements

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

Quizartinib will be supplied by the Sponsor, and efavirenz will be supplied by Worldwide Clinical Trials (Worldwide).

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

Quizartinib tablets, 30 mg: Quizartinib will be taken as a single dose of 60 mg (2 × 30 mg) (in Treatment Group A and Treatment Group B) to be administered after at least 10 hours of fasting with approximately 240 mL of water. Quizartinib will be taken in the morning. Subjects will continue to fast for 4 hours postdose.

Efavirenz tablet, 600 mg: Efavirenz will be taken once daily for 35 days (in Treatment Group A only). Efavirenz will be taken before bedtime on an empty stomach (no food for at least 2 hours before and after dosing).

6.2.3. Storage

Quizartinib tablets must be stored according to the directions on the label (store up to 25°C [77°F]; do not freeze).

Efavirenz tablets should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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.

In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

6.3. Measure to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Allocation

Subjects will be randomized in a 1:1 ratio to either Treatment Group A or Treatment Group B.

6.3.2. Blinding

This is an open-label study.

6.4. Treatment Compliance

Each dose of the study drugs will be administered by qualified study site staff. Hand and mouth checks will be performed after each dose.

6.5. Guidelines for Dose Modification

Not applicable.

6.6. Prior and Concomitant Medications

All therapies received by subjects within 28 days prior to enrollment will be recorded as prior therapies.

All therapies used from the time the subject signs the ICF for study participation to the EOS will be recorded as concomitant therapies. Concomitant therapies include all prescription, over-the-counter, and herbal remedies.

All prior and concomitant therapies will be recorded on the electronic case report form (eCRF).

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 inhibitors and inducers (see Section 10.3.2) or unless included in Section 6.8
- Hormonal replacement therapy (can be started at any time **after EOS**)
- 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 10 days 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:

- Adverse event
- Withdrawal by subject
- Investigator decision
- Pregnancy
- Protocol deviation
- Study termination 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 withdraws from the study, s/he will be required to have ET study procedures performed (refer to Section 4.1.2).

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 SoEs (Table 1.1 and Table 1.2) 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 they leave the CRU prior to the EOS and are 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 the SoEs, Table 1.1 and Table 1.2, for the procedures conducted at specific timepoints during Screening, the Treatment Period, and EOS.

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 (e.g., physical examination, electrocardiogram [ECG], and laboratory assessments) and compare against the eligibility criteria (Section 5.1 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. 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 (PK) Assessment(s)

Pharmacokinetic blood samples will be collected, processed, and shipped as detailed in the SoEs and in the Laboratory Processing Specifications as detailed in 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 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 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 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 case report form (CRF).

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, AE).
- Findings from diagnostic imaging (including computed tomography [CT] scan or other chest imaging).

8.6.2. Adverse Events

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.

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 (i.e., 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

For all randomized subjects, all AEs occurring after the subject signs the ICF and that are followed to resolution up to 30 days after the EOS, whether observed by the Investigator or reported by the subject, will be recorded as detailed in Section 10.1.6.2. 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 and recorded. All AEs (serious and non-serious) must be reported with the Investigator's assessment of seriousness, severity, and causality to the study drugs.

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 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 CRO will inform the Sponsor of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of efavirenz and quizartinib, as appropriate per institutional and/or local reporting requirements.

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.

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 or consultation with other health care professionals.

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) ≥3 × ULN and an elevated total bilirubin >2 × 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 Pointe, and Other Ventricular Arrhythmias

Subjects who experience >480 msec 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 the SAVER/Overdose Form and 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, i.e., 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 in a female subject or in a male subject's female partner that occurs while the subject is receiving or within 6 months of having received the dose of quizartinib. 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 (i.e., 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 a female subject or a 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 randomization 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 at Check-in and the results documented. For eligibility (as defined in Section 5.1), a serum pregnancy test must be performed with the results available prior to enrollment.

Women who are postmenopausal will have a follicle-stimulating hormone (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. 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.

8.6.4. Physical Examinations

Height, weight, and calculation of BMI and physical examinations will be performed as detailed in the SoEs in Section 1.3.

A full physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality in physical examination identified at baseline and any abnormalities that are changes from baseline should be recorded. 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 SoEs 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 SoEs 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. At any visit during which a subject exhibits a heart rate ≤50 bpm or other clinical indications for ECG, the ECG will be repeated. Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Whether or not the measurement is performed, the date the ECG is performed, heart rate, PR interval, RR interval, QRS amplitude, QT interval, QTcF interval, and results will be recorded.

8.7. Pharmacogenomic (Inherited Genetic) Analysis

A single blood sample for pharmacogenomic analysis will be collected predose from each randomized subject for Treatment Group A and for Treatment Group B. 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 pharmacogenomic 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 longterm preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject that consented are described in the 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 or pharmacodynamic) 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 planned for this study was not based on statistical power considerations.

With the assumed intersubject coefficient of variation (CV) of 35%, a target sample size of 30 (15/treatment) was calculated to provide 90% confidence that the estimated ratios (with and without efavirenz) of quizartinib geometric mean Cmax and AUC values would be within 20% of true population values. Therefore, 32 subjects (16 subjects in Treatment Group A and 16 subjects in Treatment Group B) will be enrolled in the study to target at least 30 subjects to complete the PK evaluation.

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 conducted on the PK Population defined as all evaluable subjects who are dosed and who have sufficient data to calculate at least 1 of the planned PK parameters.

9.4.2. Safety Population

The safety analysis will be conducted on the Safety Population defined as all subjects who receive at least 1 dose of study drug.

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. Efficacy Analysis

No efficacy measures or analysis are planned for this study.

9.5.2. Safety Analysis

9.5.2.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as new AEs that occur after the first dose 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 MedDRA dictionary. 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 CTCAE grade and relationship to study drug or AEs that were present prior to the first dose but which worsened in severity after the first dose of 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.

9.5.2.2. 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 the EOS.

Abnormal clinical laboratory results will be graded according to 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.

9.5.2.3. Electrocardiograms

Descriptive statistics will be provided for the ECG 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. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (e.g., QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤ 500 ms, and >500 ms).

A listing of ECG data will be generated.

9.5.2.4. Vital Signs

Descriptive statistics will be provided for the vital sign 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 treatment. A listing of vital sign data will be generated.

9.5.2.5. Other

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

9.5.3. Pharmacokinetics Analysis

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

9.5.3.1. Pharmacokinetic Parameters

Pharmacokinetic and statistical analysis will be performed using appropriate software; e.g., Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.). Pharmacokinetic analysis will be performed using a non-compartmental analysis (NCA) approach.

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

Cmax	Maximum concentration, determined directly from individual concentration-time data
Tmax	Time of the maximum concentration
Kel	The observed terminal rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile
t1/2	The observed terminal half-life
AUClast	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUCinf	Area under the concentration-time curve from time-zero extrapolated to infinity
AUCextr (%)	The percentage of AUCinf based on extrapolation Note: If AUCextr is greater than 20%, AUCinf and related parameters (CL/F and Vz/F) for the specific treatment will be summarized with and without subjects for whom AUCextr >20%.
Clast	The last quantifiable concentration determined directly from individual concentration-time data
Tlast	Time of the last quantifiable concentration
CL/F	Clearance after extravascular administration (for quizartinib only)
Vz/F	Volume of distribution in the terminal phase (for quizartinib only)
MPR AUClast	Metabolite-to-parent ratio for AUClast, AUClast(AC886)/AUClast
MPR AUCinf	Metabolite-to-parent ratio for AUCinf, AUCinf (AC886)/AUCinf

9.5.3.2. Statistical Analysis of Pharmacokinetic Endpoints

Plasma concentrations at each nominal timepoint and the PK parameters of quizartinib and AC886 will be summarized by Treatment Group at each nominal timepoint using descriptive

statistics: n, mean, standard deviation (SD), minimum (min), median, maximum (max), and coefficient of variation (CV%), geometric mean, and geometric CV%, as appropriate.

Cmax, AUClast, and AUCinf will be compared between Treatment Group A (quizartinib plus efavirenz; Test) and Treatment Group B (quizartinib alone; Reference). These comparisons between groups will be performed using an ANOVA model and based on logarithm-transformed Cmax, AUClast, and AUCinf. The resulting point estimates (least-squares means) differences between Treatment Group A and Treatment Group B, and 90% CIs for the difference will be exponentiated to get the ratio (Test/Reference) and corresponding 90% CI of the ratio on the untransformed scale.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the Investigator Brochure, available safety information, recruitment procedures (e.g., 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 a Coordinating Investigator. Among other possible duties, the Coordinating 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 Coordinating 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 Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

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 of which that the Investigator becomes aware.

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, the IRB, 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.

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.

For study sites in the 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 a unique subject identification as designated by the Sponsor. Documents that are not for submission to the Sponsor (e.g., 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/EC 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 (e.g., 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 the 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 (e.g., 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 randomized subject. Screen failure information will be collected at the clinical site in a log. All data collected for randomized subjects 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 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 subject identifier.

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 maintain a confidential subject identification 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 (i.e., 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 (e.g., 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, Investigator's Brochure, 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 Principal 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

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 (e.g., 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 treatment, 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	creatine phosphokinase
	albumin globulin (A/G) ratio	gamma-glutamyl transaminase (GGT)
	alanine aminotransferase (ALT)	glucose ([non-fasting/fasting])
	alkaline phosphatase (ALP)	lactate dehydrogenase
	aspartate aminotransferase (AST)	lipase
	bicarbonate/CO2	lipoprotein, high density (HDL)
	bilirubin (total)	lipoprotein, low density (LDH)
	bilirubin (direct)	magnesium (Mg)
	blood urea nitrogen (BUN)/urea	phosphorus
	calcium (Ca)	potassium (K)
	chloride (Cl)	protein (total)
	creatinine	sodium (Na)
	cholesterol (total)	triglycerides
	creatine	uric acid

Test	Analytes	
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	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 creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

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

Female:

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

10.3.2. 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 clarithromycin idelalisib nefazodone nelfinavir	Use is prohibited
Moderate	aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil	Use is prohibited

Inhibitor Type	Generic Drug Name	Allowance
Weak	chlorzoxazone cilostazol cimetidine clotrimazole fosaprepitant istradefylline ivacaftor lomitapide ranitidine ranolazine ticagrelor	Use is prohibited

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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (i.e., 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 drug-drug interaction.
- 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 (e.g., 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

A serious adverse event 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 (e.g., 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 (i.e., cannot be life-threatening or fatal), whereas sepsis can only be Grade 4

or 5 (i.e., 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 adverse event 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 (e.g., 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 (e.g., disease under study, concurrent diseases, and concomitant medications).

Determinations of causality for Treatment Group A will be categorized as follows:

- Efavirenz when administered alone
- Efavirenz and quizartinib when administered in combination

Determinations of causality for Treatment Group B will be categorized as follows:

- Quizartinib when administered alone

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 over the counter medication was required to treat the adverse event.

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

10.5. Appendix 5: Pharmacokinetic Blood Samples Collection, Processing, Storage, and Shipment

Quizartinib PK blood samples for quizartinib and AC886 will be processed as described below.

Processing Instructions	
1	Blood samples will be collected into one 4 mL Vacutainer tube containing K2-EDTA. The tube will be filled completely. The time and date of collection for each sample will be recorded.
2	Immediately after collection, the 4 mL K2-EDTA tube will be gently invert 8-10 times. **NOTE: BLOOD SAMPLES SHOULD BE KEPT AT ROOM TEMPERATURE UNTIL PLACED IN CENTRIFUGE**
3	Blood samples will be centrifuged for 10 minutes at approximately 1500-2000G at **ROOM TEMPERATURE.** Note: Samples should be centrifuged within 30 minutes of draw. There should be approximately 2 mL of plasma for each blood sample. If plasma and blood cells have not completely separated or the red blood cells suspend in the plasma, re-centrifuge the specimen for an additional 5 minutes to achieve complete separation.
4	The resulting plasma samples will be carefully aliquoted into two 3.6 mL red cryovials. - One disposable pipette should be used for each timepoint - DO NOT pour off plasma - Aliquoting should be performed immediately after completion of centrifugation - Be sure the plasma supernatant is separated carefully from the red cells without contamination
5	Cap the two 3.6 mL red cryovials and immediately freeze at -20 degrees Celsius or colder in an UPRIGHT position.
6	Samples will remain frozen until assayed.

A. Labeling of aliquot tubes

Labels will contain at least the following information:

a) Study number

b) Subject identification

c) Period or dosing phase; sampling time (relative to dosing)

B. Shipment

Prior to each study sample shipment, a shipment notification email including a minimum of the following information should be provided to the Bioanalytical Principal Investigator and Sample Management:

a) Electronic sample manifest containing all samples in the shipment

b) Name of courier or transport company

c) Shipment date and time (if available)

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

Phone: PPD

Email: PPD

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 pharmacogenomic analysis. At Screening, all potential subjects should be presented with the standard Informed Consent Form (ICF), which will include details of these procedures.

In the future, the stored sample may be used for genetic and pharmacogenomic 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) Timepoints

g) Aliquot number

B. Shipment

PGx blood samples will be shipped on dry ice.

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

PPD

PPD

Daiichi Sankyo, Inc.

211 Mt. Airy Road

Basking Ridge, NJ 07920

Phone: PPD

Mobile: PPD

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 Bioservices

Thermo Fisher Scientific

14665 Rothgeb Drive

Rockville, MD 20850

Phone: PPD

Mobile: PPD

PPD

PPD

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, 2, 4, and 8 hours postdose)	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
	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, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, 216, 288, 360, 432, and 504 hours post-quizartinib dose)	+ 60 minutes	±2 minutes (1 hour postdose)
		No more than **15** minutes after dose inclusive of the windows for ECGs and vital signs (2, 4, and 8 hours postdose)
		±15 minutes (6, 12, and 24 hours postdose)
		±30 minutes (48 through 96 hours postdose)
		±60 minutes (144 through 504 hours postdose)

11. REFERENCES

1. Zhu M et al. Model-based approach to characterize efavirenz autoinduction and concurrent enzyme induction with carbamazepine. Antimicrob Agents Chemother. 2009 Jun; 53(6): 2346–2353.
2. Altman JK et al. Phase 1 study of quizartinib in combination with induction and consolidation chemotherapy in patients with newly diagnosed acute myeloid leukemia. Am J Hematol. 2018 Feb; 93(2): 213–221.
3. "Guidance for Industry: Drug Interaction Studies–Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" Food and Drug Administration Center for Drug Evaluation and Research (CDER) February 2012.
4. Quizartinib (AC220) Investigator's Brochure. Most current version.

12. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
CDISC	clinical data interchange standards consortium
CFR	Code of Federal Regulations
Cmax	maximum concentration
CrCl	creatinine clearance
CRF	case report form
CRU	clinical research unit
CRO	contract research organization
CT	computed tomography
CTCAE	common terminology criteria for adverse events
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
GCP	good clinical practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
ICMJE	International Council of Medical Journal Editors
IMP	investigational medicinal product
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MPR	metabolite-to-parent ratio
NCI-CTCAE	National Cancer Institute - common terminology criteria for adverse events
OATP	organic anion-transporting polypeptide
OTC	over-the-counter
PCR	polymerase chain reaction
PK	pharmacokinetic
PT	prothrombin time
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SID	subject identifier
SOC	standard of care
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