CLINICAL STUDY PROTOCOL

An Open Label Study to Determine the Absolute Oral Bioavailability of Quizartinib Using a Radiolabeled Microtracer in Healthy Subjects

Absolute Bioavailability of Quizartinib

PROTOCOL NUMBER: AC220-A-U107 (QSC203118)

EUDRACT NUMBER: 2021-000198-10

NCT NUMBER: NCT04796831

IND NUMBER: 074552

VERSION 2.0, 23 Mar 2021

DAIICHI SANKYO, INC

211 Mount Airy Road

Basking Ridge, New Jersey 07920

DOCUMENT HISTORY

Version Number	Version Date
1.0	08 Feb 2021
2.0	23 Mar 2021

INVESTIGATOR AGREEMENT

An Open Label Study to Determine the Absolute Oral Bioavailability of Quizartinib Using a Radiolabeled Microtracer in Healthy Subjects

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
PPD	3/23/2021
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

PPD	PPD
Print Name	**Signature**
PPD	3/23/2021
Title	**Date (DD MMM YYYY)**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
An Open Label Study to Determine the Absolute Oral Bioavailability of Quizartinib Using a Radiolabeled Microtracer in Healthy Subjects
Protocol Short Title
Absolute Bioavailability of Quizartinib
Protocol Number
AC220-A-U107 (QSC203118)
Sponsor/Collaborators
Daiichi Sankyo, Inc.
Registry Identification(s)
• EudraCT Number: 2021-000198-10 • NCT Number: NCT04796831
IND Number
074552
Study Phase
Phase 1
Planned Geographical Coverage, Study Site and Location
United Kingdom (UK), 1 Site, Nottingham (Quotient Sciences, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK, Tel: +44 (0)115 974 9000)
Study Population
Healthy male subjects 18 years to 55 years of age (inclusive), with a body mass index (BMI) of 18.0 kg/m^2 to 32.0 kg/m^2 (inclusive) at screening
Study Objectives/Outcome Measures and Endpoints
The table below lists primary, secondary, and exploratory study objectives and endpoints that have outcome measures.

Objectives	Outcome Measure	Category
Primary		
• To determine the absolute oral bioavailability of quizartinib.	• Absolute bioavailability assessment based on the pharmacokinetic (PK) parameters AUClast and AUCinf for quizartinib following intravenous (IV) and oral administrations.	PK
Secondary		
• To characterize the plasma PK of quizartinib and ^{14}C-quizartinib following a single, oral dose of 60 mg quizartinib and a single, IV	• Plasma PK parameters for quizartinib following the single oral dose: Cmax, Tmax, t1/2, AUClast, AUCinf, CL/F and Vz/F.	PK

administration of 50 µg ^{14}C-quizartinib.	• Plasma PK parameters for ^{14}C-quizartinib following the single IV administration: Cmax, Tmax, t1/2, AUClast, AUCinf, CL and Vz.	
• To characterize the plasma PK of the major circulating metabolite, AC886, and ^{14}C-AC886 following a single, oral dose of 60 mg quizartinib and a single, IV administration of 50 µg ^{14}C-quizartinib.	• Plasma PK parameters for both AC886 and ^{14}C-AC886: Cmax, Tmax, t1/2, AUClast, AUCinf, metabolite to parent ratio (MPR) based on AUC (area under the curve).	PK
• To characterize the plasma PK of total radioactivity following a single, IV administration of 50 µg ^{14}C-quizartinib.	• Plasma PK parameters for total radioactivity: AUClast, AUCinf, t1/2.	PK
• To assess the safety and tolerability of a single dose of quizartinib in healthy subjects.	• Adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), physical examinations.	Safety
Exploratory		
• To assess the fecal and urinary recovery of total radioactivity following a single, IV administration of 50 µg ^{14}C-quizartinib.	• Amount of total radioactivity excreted in urine and feces (Ae). • Amount of total radioactivity excreted in feces and urine as a fraction of the administered IV dose (Fe).	PK
• To assess the fecal and urinary recovery of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.	• Amount of quizartinib and AC886 excreted in urine and feces (Ae). • Amount of quizartinib and AC886 excreted in feces and urine as a fraction of the administered oral dose (Fe).	PK
• To characterize the whole blood PK of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.	• Whole blood PK parameters for quizartinib: Cmax, Tmax, AUClast, AUCinf, t1/2, CL/F and Vz/F. • Whole blood PK parameters for AC886: Cmax, Tmax, AUClast, AUCinf and t1/2.	PK
• To determine whole blood-to-plasma concentration ratios (Kbp) of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.	• Kbp based on whole blood and plasma concentrations of quizartinib and AC886.	PK

Study Design

This is a single center, open-label, Phase 1 study to determine the absolute oral bioavailability in healthy male subjects. It is planned to enroll 8 subjects to ensure data in a minimum of 6 subjects who are evaluable for PK. An evaluable subject is defined as a subject who has received both the oral and IV microtracer investigational medicinal products (IMPs; i.e., a single, oral dose of 60 mg quizartinib dihydrochloride tablets [2 x 30 mg tablets] and an IV administration of 50 µg ^{14}C-quizartinib solution for infusion 10 µg/mL containing not more than [NMT] 22.84 kBq ^{14}C in 5 mL [NMT 4.6 kBq/mL] over 15 minutes at 4 hours post-oral dose) and has sufficient samples for evaluation of plasma PK parameters.

Each subject will receive a single, oral dose of 60 mg quizartinib dihydrochloride tablets (administered as 2 x 30 mg tablets) and a single, IV administration of 50 µg ^{14}C-quizartinib solution for infusion containing NMT 22.84 kBq ^{14}C in 5 mL (NMT 4.6 kBq/mL), administered as an infusion over 15 minutes beginning at 4 hours post-oral dosing. Both IMPs will be administered in the fasted state.

Subjects will undergo preliminary screening procedures for the study up to 21 days before IMP administration (Day -21 to Day-2). Subjects will be admitted in the morning on the day prior to IMP administration (i.e., Day -1), at which time admission procedures will be undertaken to confirm eligibility. Subjects will be

dosed in the morning of Day 1 following an overnight fast of a minimum of 8 hours for the oral dose (a minimum of 12 hours for the IV dose).

To assess tolerability of the IV administration, dosing will be staggered. The first subject will receive the oral dose at least 30 minutes prior to the second subject. All subsequent dosing will be staggered by at least 15 minutes. The IV administration will start at 4 hours post-oral dosing for all subjects, and will therefore be staggered as well.

Blood, urine and fecal samples will be collected pre-dose and at regular intervals until Day 22 for PK analysis. Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

Subjects will remain resident in the clinical unit until 504 hours post-oral dose (i.e., Day 22) when they will be discharged from the clinical unit. Safety discharge assessments will be performed at the time of actual discharge from the clinical unit; discharge PK samples will be collected at 504 hours post-oral dose or at time of actual discharge if earlier (i.e., due to early termination [ET]/withdrawal).

If a subject reports any AEs between discharge and 7 days post-discharge (i.e., between Day 22 and Day 29) that represent a cause for concern, they will be required to attend the clinical unit for a follow-up assessment as per the discretion of the Investigator or delegate. This will be an unscheduled visit.

Study Duration

Subjects will receive a single oral dose of 60 mg quizartinib dihydrochloride tablets and a single IV dose of 50 µg ^{14}C-quizartinib solution for infusion at 4 hours post-oral dosing on a single occasion during this study. The estimated time from screening until discharge from the study is approximately 6 weeks.

Key Eligibility Criteria

Key Inclusion Criteria:

Healthy males aged 18 years to 55 years of age (inclusive) at the time of signing informed consent.

Body mass index (BMI) of 18.0 kg/m^2 to 32.0 kg/m^2 (inclusive) at screening

Key Exclusion Criteria:

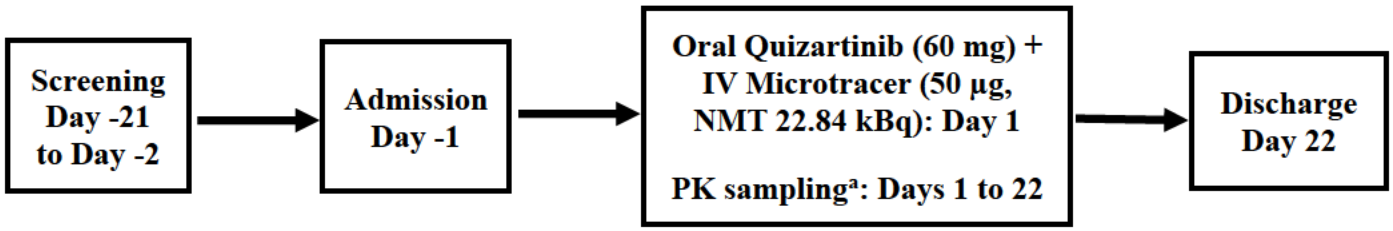
Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key exclusion criteria:

- History or presence of:
  - Clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal (GI), endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, as judged by the Investigator.
  - 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 admission (Day -1), of any of the following cardiac conduction abnormalities:
  - QT interval corrected with Fridericia's formula (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).
- Laboratory results (serum chemistry, hematology, coagulation, and urinalysis) outside the normal range, if considered clinically significant by the Investigator at screening or admission (Day -1).
- Estimated creatinine clearance (CrCl) <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 admission (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
The treatment will be a single, oral dose of 60 mg quizartinib dihydrochloride tablets (2 x 30 mg tablets) with an IV administration of 50 µg ^{14}C-quizartinib solution for infusion 10 µg/mL containing NMT 22.84 kBq ^{14}C in 5 mL (NMT 4.6 kBq/mL) over 15 minutes at 4 hours post-oral dose. Oral dose of 60 mg quizartinib dihydrochloride tablets (2 x 30 mg tablets) to be administered following an overnight fast of a minimum of 8 hours with 240 mL of water. Subjects will continue to fast for 4 hours post-oral dose (i.e., until administration of the IV dose is complete).
Active Ingredient
Quizartinib dihydrochloride
Planned Sample Size
The number of subjects planned for this study was not based on statistical power calculations. 8 subjects will be enrolled in the study to target at least 6 subjects to complete the PK evaluation (i.e., to allow for withdrawal or non-PK evaluability in up to 2 dosed subjects).

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



IV: intravenous, NMT: not more than, PK: pharmacokinetic
[a] PK sampling includes whole blood, plasma, urine and fecal samples as indicated in the Schedule of Events (SoE)

1.3. Schedule of Events

Table 1.1: Schedule of Events

Study Period	**Screening**	**Pre-Admission (if required)**	***Residency In Clinic***																	
			Admission	**1**												**2**	**3**	**4**	**5**	
Study Day	**-21 to -2**	**-2**	**-1**																	
Time Point Relative to Oral Dosing (hours)[a]				**Pre-dose**	**0**	**1**	**2**	**4**	**4.25**	**4.5**	**4.75**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**96**	
Time Point Relative to Start of IV Infusion (hours)					**-4**	**-3**	**-2**	**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**8**	**20**	**44**	**68**	**92**	
Informed Consent	X																			
Inclusion/Exclusion Criteria	X		X[b]	X[b]																
Vein Assessment	X																			
Demographic Information	X																			
Medical/Surgical History	X		X[c]																	
Complete Physical Examination	X																			
Targeted (symptom driven) Physical Examination[d]			X																	
Body Weight, Height and BMI[e]	X		X																	
Alcohol Breath Test	X		X																	
SARS-CoV-2 Antibody[f]	X																			
SARS-CoV-2 Antigen[f]	X	X																		
Urine Drugs of Abuse, Cotinine	X		X																	

BMI: body mass index, COVID-19: coronavirus disease 2019, IV: intravenous, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

[a] All assessments will be timed and performed relative to the start of oral dosing.
[b] Eligibility will be re-assessed at admission/pre-dose.
[c] Update only.
[d] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the Investigator's judgement.
[e] Height to be measured and BMI to be calculated at screening only.
[f] Testing for SARS-CoV-2 will be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction (PCR) test or other antigen test performed at screening, the day before admission (i.e., Day -2), and discharge (i.e., Day 22). The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick-Off Meeting minutes.

Table 1.1 Continued: Schedule of Events

Study Period	**Screening**	**Pre-Admission (if required)**	***Residency In Clinic***																
			Admission	**1**												**2**	**3**	**4**	**5**
Study Day	**-21 to -2**	**-2**	**-1**																
Time Point Relative to Oral Dosing (hours)[a]				**Pre-dose**	**0**	**1**	**2**	**4**	**4.25**	**4.5**	**4.75**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**96**
Time Point Relative to Start of IV Infusion (hours)					**-4**	**-3**	**-2**	**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**8**	**20**	**44**	**68**	**92**
Virology (HBsAg/HIV/HAV/HCV)	X																		
Hematology, Serum Chemistry[g]	X		X																X
Estimated creatinine clearance (CrCl)[h]	X																		
Urinalysis	X		X																X
Coagulation (aPTT, PT, INR)	X		X	X															X
12-lead ECGs[i]	X		X	X			X	X[j]								X		X	
Vital Signs[k]	X		X	X			X	X[j]								X		X	
IMP Administration[l]					X			X											
Plasma PK samples for quizartinib and AC886				X		X	X	X[m]	X	X	X	X	X	X	X	X	X	X	X

[14]C: carbon-14, aPTT: activated partial thromboplastin time, ECG: electrocardiogram, HAV: hepatitis A virus, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, HIV: human immunodeficiency virus, IMP: investigational medicinal product, INR: international normalized ratio, IV: intravenous, PK: pharmacokinetic, PT: prothrombin time

[a] All assessments will be timed and performed relative to the start of oral dosing.
[g] Samples for serum chemistry will be collected after a 8 hour fast.
[h] The estimated creatinine clearance (CrCl; mL/min) will be calculated at screening from serum creatinine using the Cockcroft-Gault equation.
[i] 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 prior to the blood collection.
[j] Assessment to be performed prior to the start of the IV infusion.
[k] Blood pressure, heart rate, respiratory rate and oral temperature will be measured at all time points after at least a 5 minutes supine rest.
[l] A single, oral dose of 60 mg quizartinib will be administered following an overnight fast of a minimum of 8 hours on Day 1 and a single, IV administration of 50 µg ^{14}C-quizartinib containing NMT 22.84 kBq ^{14}C will be administered as an infusion over 15 minutes beginning at 4 hours post-oral dosing (also in the fasted state). This infusion will be in the opposite arm being used for PK sampling.
[m] Sample to be taken prior to the start of the IV infusion.

Table 1.1 Continued: Schedule of Events

Study Period	**Screening**	**Pre-Admission (if required)**	***Residency In Clinic***																
			Admission	**1**												**2**	**3**	**4**	**5**
Study Day	**-21 to -2**	**-2**	**-1**																
Time Point Relative to Oral Dosing (hours)[a]				**Pre-dose**	**0**	**1**	**2**	**4**	**4.25**	**4.5**	**4.75**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**96**
Time Point Relative to Start of IV Infusion (hours)					**-4**	**-3**	**-2**	**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**8**	**20**	**44**	**68**	**92**
Plasma PK samples for total radioactivity, ^{14}C-quizartinib and ^{14}C-AC886								X[n]	X	X	X	X	X	X	X	X	X	X	X
Whole blood PK samples for quizartinib and AC886				X		X	X	X[m]	X	X	X	X	X	X	X	X	X	X	X
Urine Samples for total radioactivity, quizartinib and AC886[o]			←----------X----------→																
Fecal Samples for total radioactivity, quizartinib and AC886[p]			←----------X----------→																
Pharmacogenomic Blood Sample				X															
Adverse Event Monitoring	←----------X----------→																		
Prior/Concomitant Medications	←----------X----------→																		
Clinic Confinement			←----------X----------→																

^{14}C: carbon-14, IV: intravenous, PK: pharmacokinetic

[a] All assessments will be timed and performed relative to the start of oral dosing.
[m] Sample to be taken prior to the start of the IV infusion.
[n] Pre-dose sample for total radioactivity, ^{14}C-quizartinib and ^{14}C-AC886. Sample to be taken prior to the start of the IV infusion.
[o] The pre-dose urine sample will be taken any time between admission and pre-dose. Post-dose urine samples will be taken at the following collection periods: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours post-oral dose and then daily (24 hour intervals) until discharge at 504 hours post-oral dose (Day 22).
[p] The pre-dose fecal sample can be collected any time between admission and pre-dose. Post-dose fecal samples will be collected at 24 hour intervals post-oral dosing.

Table 1.1 Continued: Schedule of Events

Study Period	***Residency In Clinic***																
Study Day	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22 (ET/ Discharge)[q]**
Time Point Relative to Oral Dosing (hours)[a]	**120**	**144**	**168**	**192**	**216**	**240**	**264**	**288**	**312**	**336**	**360**	**384**	**408**	**432**	**456**	**480**	**504**
Time Point Relative to Start of IV Infusion (hours)	**116**	**140**	**164**	**188**	**212**	**236**	**260**	**284**	**308**	**332**	**356**	**380**	**404**	**428**	**452**	**476**	**500**
Targeted (symptom driven) Physical Examination[d]																	X
Body Weight, Height and BMI[e]																	X
SARS-CoV-2 Antigen[f]																	X
Hematology, Serum Chemistry[g]																	X
Urinalysis																	X
Coagulation (aPTT, PT, INR)																	X
12-lead ECGs[i]																	X
Vital Signs[k]																	X
Plasma PK samples for quizartinib and AC886		X		X		X		X		X		X		X		X	X

aPTT: activated partial thromboplastin time, BMI: body mass index, COVID-19: coronavirus disease 2019, ECG: electrocardiogram, ET: early termination, INR: international normalized ratio, IV: intravenous, PK: pharmacokinetic, PT: prothrombin time, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

[a] All assessments will be timed and performed relative to the start of oral dosing.
[d] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the Investigator's judgement.
[e] Height to be measured and BMI to be calculated at screening only.
[f] Testing for SARS-CoV-2 will be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction (PCR) test or other antigen test performed at screening, the day before admission (i.e., Day -2), and discharge (i.e., Day 22). The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.
[g] Samples for serum chemistry will be collected after an 8 hour fast.
[i] 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 prior to the blood collection.
[k] Blood pressure, heart rate, respiratory rate and oral temperature will be measured at all time points after at least a 5 minutes supine rest.
[q] Discharge from the clinical unit will follow final blood sample collections; the same procedures are to be performed at early termination/withdrawal as at discharge.

Table 1.1 Continued: Schedule of Events

Study Period	***Residency In Clinic***																
Study Day	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22 (ET/ Discharge)[q]**
Time Point Relative to Oral Dosing (hours)[a]	**120**	**144**	**168**	**192**	**216**	**240**	**264**	**288**	**312**	**336**	**360**	**384**	**408**	**432**	**456**	**480**	**504**
Time Point Relative to Start of IV Infusion (hours)	**116**	**140**	**164**	**188**	**212**	**236**	**260**	**284**	**308**	**332**	**356**	**380**	**404**	**428**	**452**	**476**	**500**
Plasma PK samples for total radioactivity, ^{14}C-quizartinib and ^{14}C-AC886		X		X		X		X		X		X		X		X	X
Whole blood PK samples for quizartinib and AC886		X		X		X		X		X		X		X		X	X
Urine Samples for total radioactivity, quizartinib and AC886[o]	←----------X----------→																
Fecal Samples for total radioactivity, quizartinib and AC886[p]	←----------X----------→																
Adverse Event Monitoring	←----------X----------→																
Prior/Concomitant Medications	←----------X----------→																
Clinic Confinement	←----------X----------→																

^{14}C: carbon-14, IV: intravenous, PK: pharmacokinetic

[a] All assessments will be timed and performed relative to the start of oral dosing.
[o] The pre-dose urine sample will be taken any time between admission and pre-dose. Post-dose urine samples will be taken at the following collection periods: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours post-oral dose and then daily (24 hour intervals) until discharge at 504 hours post-oral dose (Day 22).
[p] The pre-dose fecal sample can be collected any time between admission and pre-dose. Post-dose fecal samples will be collected at 24 hour intervals post-oral dosing.
[q] Discharge from the clinical unit will follow final blood sample collections; the same procedures are to be performed at early termination/withdrawal as at discharge.

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 FLT3-internal tandem duplication (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 in healthy subjects under fasting conditions, the peak exposure of quizartinib and its major circulating active metabolite (AC886) occurs at a median of approximately 4 hours (range: 2 hours to 8 hours) and 5 hours (range: 4 hours to 120 hours) post-dose, 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 area under the curve (AUC) exposure was approximately 60% of the parent steady state exposure. In vitro reaction phenotyping using human liver microsomes and recombinant human cytochrome P450 (CYP) enzymes showed that both quizartinib and AC886 are primarily metabolized by CYP3A and have estimated effective half-lives (t1/2) of 73 hours and 119 hours, respectively. Additionally, AC886 is also formed from quizartinib by CYP3A.

In a clinical absorption, distribution, metabolism, and elimination (ADME) study (AC220-006), a single oral dose of 60 mg carbon-14 (^{14}C)-quizartinib containing approximately 100 µCi (3.7 MBq) ^{14}C was administered to healthy male subjects. Approximately 76% of the radioactive dose was recovered in feces, and 1.6% of the dose was recovered in urine at study completion at 14 days post-dose. Since <2% of the total dose was excreted in urine, quizartinib is eliminated primarily by hepatobiliary pathways. The major circulating components were the unchanged parent (quizartinib) and the oxidative metabolite (AC886), which represented more than 10% of the total radioactivity exposure in plasma.

In a hepatic impairment (HI) study (AC220-016) in subjects with mild and moderate HI as defined by Child Pugh score, quizartinib overall exposure (AUC from the time of dosing extrapolated to infinity [AUCinf]) increased approximately 30% and 15%, 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. Use of a strong CYP3A inhibitor (ketoconazole) and a moderate CYP3A inhibitor (fluconazole) increased quizartinib AUC by 96% and 20%, respectively. Strong CYP3A inducer rifampin decreased quizartinib AUC by approximately 70%; however, due to bioanalytical issue, the results were not quantitatively conclusive.

As of 28 Oct 2020, a total of 2,215 subjects had received quizartinib in 26 clinical studies: 1673 subjects with AML, 13 subjects with solid tumors, 21 subjects with mild/moderate hepatic

impairment, and 508 healthy volunteers. In addition, 798 subjects have been treated in 10 investigator-initiated studies.

In 11 studies in healthy volunteers or subjects with HI, quizartinib was generally well tolerated as single doses ranging from 20 mg to 90 mg, with most adverse events (AEs) of mild severity. Four subjects experienced severe AEs. In Study AC220-014, there were 2 Grade 3 AEs experienced in 2 subjects. One treatment-emergent adverse event (TEAE) of increased alanine aminotransferase (ALT) resolved without treatment. The second Grade 3 AE was a serious adverse event (SAE) of limb abscess. The subject required hospitalization and was withdrawn from the study due to this event. Neither AE was considered related to study drug. In Study AC220-019, 1 subject experienced a Grade 3 elevation of blood creatine phosphokinase. The event was considered not related to study drug. In Study AC220-015, 1 subject had a Grade 3 AE of musculoskeletal stiffness of the neck. The AE was considered not related to any of the study drugs (quizartinib, ketoconazole, or rifampin) and resolved in 15 days.

2.2. Study Rationale

Quizartinib, a selective FLT3 inhibitor, is being developed as a treatment for AML and MDS. The absolute oral bioavailability of quizartinib has not yet been studied. Therefore, this study is designed to estimate quizartinib bioavailability based on the dose-adjusted exposure of quizartinib following oral and intravenous (IV) administration.

Knowing the absolute bioavailability of an oral drug product is a regulatory requirement in some regions. In addition, understanding the bioavailability of a drug and the factors that influence absorption, may guide the formulation development strategy and risk assessment for drug-drug interactions.

As this is a Phase 1 study assessing the absolute bioavailability, pharmacokinetic (PK) and safety of quizartinib, the most relevant population is healthy volunteers, as recommended by the United States (US) Food and Drug Administration (FDA) (1) and the European Medicines Agency (EMA) (2). Subjects who are non-smokers without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

There are no human data on the effect of quizartinib on fertility. Based on findings in animals, female and male fertility may be impaired with treatment with quizartinib. Fetotoxicity and teratogenicity in rats has also been observed. Therefore, female subjects will not be enrolled in this study. In addition, subjects with pregnant or lactating partners will be excluded from the study.

2.3. Benefit and Risk Assessment

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

2.3.1. Risks Associated with the Oral Quizartinib Dose

In the clinical program, as of 28 Oct 2020, a total of 2,215 subjects had received quizartinib in 26 clinical studies: 1673 subjects with AML, 13 subjects with solid tumors, 21 subjects with mild/moderate hepatic impairment, and 508 healthy volunteers. In addition, 798 subjects have

been treated in 10 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. Toxicities observed for quizartinib in healthy subjects following single dose administration included those in the system organ classes of Gastrointestinal Disorders (e.g., constipation, diarrhea, and gastroesophageal reflux disease), Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, and Nervous System Disorders (e.g., headache and dysgeusia). Most AEs were mild in severity.

Quizartinib is associated with QT prolongation in a dose dependent manner. The incidence of QT prolongation (corrected QT interval using Fridericia's formula ([QTcF]) >500 ms was 3% to 5% among subjects with AML receiving 30 mg to 60 mg quizartinib daily, 15% to 17% among subjects receiving 90 mg to 135 mg quizartinib daily, and 35% among 17 subjects receiving 200 mg quizartinib daily. The concentration-corrected QT interval (C QTc) analysis demonstrated that quizartinib, not AC886, is the primary contributor to QT prolongation. Corrected QT interval (QTc) interval prolongation is a risk factor for the development of cardiac arrythmias, including Torsade de Pointes (TdP).

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 electrocardiogram (ECG) data; there were no cases of 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.

Other adverse reactions to quizartinib, observed in patients with AML include cytopenias (leukopenia, anemia, thrombocytopenia, neutropenia, febrile neutropenia, pancytopenia, lymphopenia) and associated disorders of infection and bleeding, gastrointestinal (GI) disorders (abdominal pain, nausea, vomiting, diarrhea, dyspepsia, dysgeusia, stomatitis, and decreased appetite), general disorders (pyrexia, fatigue, asthenia, malaise, weight decreased, and edema peripheral), skin rash, petechiae, acute febrile neutrophilic dermatosis, electrolyte abnormalities (hypokalemia and hypomagnesemia), liver function test abnormalities (ALT increased, increased aspartate aminotransferase [AST], increased blood alkaline phosphatase, increased blood bilirubin). In addition, embryo-fetal toxicity and impaired fertility are considered potential risks for quizartinib.

The nonclinical safety program for quizartinib, which includes its active metabolite AC886, has been conducted using both in vitro and in vivo systems (mice, rats, rabbits, guinea pigs, dogs, and monkeys) in pharmacological, PK, and toxicological studies (including single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, juvenile toxicity, antigenicity, and photo safety studies). Notably, quizartinib was not phototoxic in the in vitro neutral red uptake (NRU) phototoxicity test with Balb/c 3T3 mouse fibroblasts and therefore restrictions relating to phototoxicity will not be required in this study. However, studies in rats and monkeys suggested quizartinib may cause male and female fertility impairment, fetotoxicity

and teratogenicity; therefore, females and male subjects with pregnant or lactating partners will not be enrolled in this study.

Please refer to the most recent version of the Investigator's Brochure (IB) for the risks associated with quizartinib (3).

2.3.2. Risks Associated with the Intravenous ^{14}C-Quizartinib Microdose

The IV (infused) microdose to be administered is 1200-fold lower than the oral dose and the exposure to quizartinib originating from the infused microdose is therefore considered negligible and no AEs are expected to occur.

Although subjects in this study are exposed to ionizing radiation, the amount is negligible. The radiation dose from a dose of not more than (NMT) 22.84 kBq will result in an effective dose of 12.79 microsievert (µSv), falling into International Commission on Radiological Protection (ICRP) Category I. The United Kingdom (UK) average radiation exposure for an individual is about 2.7 mSv (= 2,700 µSv; data obtained from Public Health England [PHE] Ionising Radiation Exposure of the UK Population: 2010 Review) per year and as such the radiation risk to subjects in this study is considered negligible.

2.3.3. COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the time in which the study is conducted during the coronavirus disease 2019 (COVID-19) pandemic.

Against the background of the COVID-19 pandemic, the potential risk of a subject developing COVID-19 has been considered in terms of the risk-benefit evaluation.

As described in the IB, AEs associated with immune systems disorders have been reported following administration of quizartinib (3). Therefore, the study includes several features to mitigate any potential risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection:

- The study entry criteria that exclude subjects with current infections or exaggerated risk of infection (see Section 5.2).
- Subjects must be otherwise healthy and aged ≤55 years; persons in this demographic are intrinsically less vulnerable to symptomatic infection by SARS-CoV-2 and its clinical sequelae (4, 5, 6).
- The clinical research unit (CRU) has implemented standard operating procedures (SOPs) for risk mitigation as outlined in Section 2.3.3.1.
- The protocol excludes subjects with any evidence of current SARS-CoV-2 infection (see Sections 5.2 and 7.1) in order to prevent subjects who are shedding the virus from entering into the CRU, and from being dosed with quizartinib.
- Subjects will be resident in the clinic until 21 days post-oral dose. This allows sufficient time for the compound to be cleared from the body before subjects leave the CRU and are exposed to ambient SARS-CoV-2 in the community.

2.3.3.1. General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with the contract research organization (CRO)'s (i.e., Quotient Sciences [hereafter referred to as Quotient]s') monitoring and prevention control measures.

COVID-19 testing will be performed based on current infection rates and availability of tests. Testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction (PCR) test or other antigen test performed at screening, the day before admission, and discharge or the day before discharge. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on the processes for COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick Off Meeting minutes.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

2.3.3.2. COVID-19 Vaccine-Related Risk

Following the granting of the conditional (temporary) marketing authorization of the COVID-19 vaccines by the UK Medicines and Healthcare products Regulatory Agency (MHRA), e.g., Pfizer and BioNTech's vaccine, Oxford-AstraZeneca vaccine, these vaccines may be permitted according to the Investigator's discretion and per local guidance. In this study, a washout period of 72 hours prior to investigational medicinal product (IMP; i.e., quizartinib – an RTK inhibitor) administration has been recommended to minimize the possibility of any drug-drug interactions between the IMP and the vaccine.

Based on the mechanism of action of the IMP (quizartinib), as a RTK inhibitor, there is no perceived impact on the safety of the study subjects or on the study objectives for subjects who may receive these vaccines (either first or second doses). It is also unlikely that administration of the IMP would interfere with COVID-19 vaccination response; however, no specific preclinical or clinical investigations have been conducted at this point with quizartinib.

The emerging safety and efficacy data from millions of vaccinated people, many of whom are elderly and with underlying health conditions and taking multiple concomitant medications, indicate that these vaccines have a good safety and efficacy record. In the broader interests of society and to limit the extent of the global pandemic, it is important that subjects should receive a vaccine when it is offered to them.

2.3.4. General Risks

Collecting a blood sample from a vein may cause pain, swelling, bruising, light headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick. Usually these changes are mild, transient and resolve within a few days to weeks without any intervention.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram (ECG) stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

3.1. Primary Objective/Endpoints

The primary objective of this study is:

- To determine the absolute oral bioavailability of quizartinib.

The primary endpoints of this study are:

- Absolute bioavailability assessment based on the PK parameters AUClast and AUCinf for quizartinib following IV and oral administrations.

3.2. Secondary Objectives/Endpoints

The secondary objectives of this study are:

- To characterize the plasma PK of quizartinib and ^{14}C-quizartinib following a single, oral dose of 60 mg quizartinib and a single, IV administration of 50 µg ^{14}C-quizartinib.
- To characterize the plasma PK of the major circulating metabolite, AC886, and ^{14}C-AC886 following a single, oral dose of 60 mg quizartinib and a single, IV administration of 50 µg ^{14}C-quizartinib.
- To characterize the plasma PK of total radioactivity following a single, IV administration of 50 µg ^{14}C-quizartinib.
- To assess the safety and tolerability of a single dose of quizartinib in healthy subjects.

The secondary endpoints of this study are:

- Plasma PK parameters for quizartinib following the single oral dose: Cmax, Tmax, t1/2, AUClast, AUCinf, CL/F and Vz/F.
- Plasma PK parameters for ^{14}C-quizartinib following the single IV administration: Cmax, Tmax, t1/2, AUClast, AUCinf, CL and Vz.
- Plasma PK parameters for both AC886 and ^{14}C-AC886: Cmax, Tmax, t1/2, AUClast, AUCinf, metabolite to parent ratio (MPR) based on AUC.
- Plasma PK parameters for total radioactivity: AUClast, AUCinf, t1/2.
- AEs, vital signs, 12-lead ECGs, clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), physical examinations.

3.3. Exploratory Objectives/Endpoints

The exploratory objective of this study is:

- To assess the fecal and urinary recovery of total radioactivity following a single, IV administration of 50 µg ^{14}C-quizartinib.
- To assess the fecal and urinary recovery of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.

- To characterize the whole blood PK of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.
- To determine whole blood-to-plasma concentration ratios (Kbp) of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib.

The exploratory endpoints of this study are:

- Amount of total radioactivity excreted in urine and feces (Ae).
- Amount of total radioactivity excreted in feces and urine as a fraction of the administered IV dose (Fe).
- Amount of quizartinib and AC886 excreted in urine and feces (Ae).
- Amount of quizartinib and AC886 excreted in feces and urine as a fraction of the administered oral dose (Fe).
- Whole blood PK parameters for quizartinib: Cmax, Tmax, AUClast, AUCinf, t1/2, CL/F and Vz/F.
- Whole blood PK parameters for AC886: Cmax, Tmax, AUClast, AUCinf and t1/2.
- Kbp based on whole blood and plasma concentrations of quizartinib and AC886.

4. STUDY DESIGN

4.1. Overall Design

This is a single center, open-label, Phase 1 study to determine the absolute oral bioavailability in healthy male subjects. It is planned to enroll 8 subjects to ensure data in a minimum of 6 subjects who are evaluable for PK. An evaluable subject is defined as a subject who has received both the oral and IV microtracer IMPs (i.e., a single, oral dose of 60 mg quizartinib dihydrochloride tablets [2 x 30 mg tablets] and an IV administration of 50 µg ^{14}C-quizartinib solution for infusion 10 µg/mL containing NMT 22.84 kBq ^{14}C in 5 mL [NMT 4.6 kBq/mL] over 15 minutes at 4 hours post-oral dose) and has sufficient samples for evaluation of plasma PK parameters.

4.1.1. Design Overview

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

Subjects will undergo preliminary screening procedures for the study up to 21 days before IMP administration (Day -21 to Day-2). Subjects will be admitted in the morning on the day prior to IMP administration (i.e., Day -1), at which time admission procedures will be undertaken to confirm eligibility. Subjects will be dosed in the morning of Day 1 following an overnight fast of a minimum of 8 hours for the oral dose (a minimum of 12 hours for the IV dose).

To assess tolerability of the IV administration, dosing will be staggered. The first subject will receive the oral dose at least 30 minutes prior to the second subject. All subsequent dosing will be staggered by at least 15 minutes. The IV administration will start at 4 hours post-oral dosing for all subjects, and will therefore be staggered as well.

Blood, urine and fecal samples will be collected pre-dose and at regular intervals until Day 22 for PK analysis. Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

4.1.2. End-of-Study

Subjects will remain resident in the clinical unit until 504 hours post-oral dose (i.e., Day 22) when they will be discharged from the clinical unit. Safety discharge assessments will be performed at the time of actual discharge from the clinical unit; discharge PK samples will be collected at 504 hours post-oral dose or at time of actual discharge if earlier (i.e., due to early termination [ET]/withdrawal; see Sections 7.1 and 7.2).

If a subject reports any AEs between discharge and 7 days post-discharge (i.e., between Day 22 and Day 29) that represent a cause for concern, they will be required to attend the clinical unit for a follow-up assessment as per the discretion of the Investigator or delegate. This will be an unscheduled visit.

The end of the study is defined as the last visit of the last subject (e.g., follow-up assessment). Any changes to this definition will be notified as a substantial amendment.

The MHRA and Ethics Committee (EC) should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

The Administration of Radioactive Substances Advisory Committee (ARSAC) and the ARSAC Practitioner will also be notified of the end of trial or ET of the trial in writing within an appropriate timeframe.

4.1.3. Dose Regimen

Each subject will receive a single, oral dose of 60 mg quizartinib dihydrochloride tablets (administered as 2 x 30 mg tablets) and a single, IV administration of 50 µg ^{14}C-quizartinib solution for infusion containing NMT 22.84 kBq ^{14}C in 5 mL (NMT 4.6 kBq/mL), administered as an infusion over 15 minutes beginning at 4 hours post-oral dosing. Both IMPs will be administered in the fasted state.

4.1.4. Duration

Subjects will receive a single oral dose of 60 mg quizartinib dihydrochloride tablets and a single IV dose of 50 µg ^{14}C-quizartinib solution for infusion at 4 hours post-oral dosing on a single occasion during this study. The estimated time from screening until discharge from the study is approximately 6 weeks.

4.2. Rationale for Study Design

The IV microtracer technique is an established methodology for measuring the IV and oral kinetics of a drug in the same individuals in a single dosing period. The technique involves concurrent administration of a microdose of the drug containing microtracer amounts of ^{14}C with a single oral therapeutic dose, which avoids the concerns of dose dependent kinetics when extrapolating IV PK from a microdose, as the systemic exposure is at therapeutic concentrations. Moreover, for this reason the IV administration is timed to coincide with the expected Tmax of the oral dose. This technique also enables a lower dose to be administered intravenously compared to the oral dose (which is advantageous from a safety perspective), and allows for dose adjustment for the purposes of absolute bioavailability calculation. This design enables measurement of ^{14}C labelled drug in plasma following IV dosing via sensitive accelerator mass spectrometry (AMS) techniques, and measurement of the unlabeled parent in the plasma by standard high-performance liquid chromatography mass spectrometry/mass spectrometry (HPLC MS/MS) techniques. Thus, it is possible to obtain the IV PK parameters with the associated variability, and calculate the absolute bioavailability. In addition, because the IV dose administration involves giving a low volume of a low concentration of parent drug, an advantage of this approach is that it is much easier to develop an IV formulation for microdosing, than it would be for a higher clinical dose. Moreover, by administering the IV formulation as a microdose, this avoids any exposure-related safety concerns that could potentially arise from administering a 60 mg dose of quizartinib intravenously.

The effect of food on the PK of quizartinib has been investigated in previous clinical studies in healthy subjects and was suggested to be minimal (based on Cmax, AUClast and AUCinf). Administration of quizartinib in the fed state delayed quizartinib absorption compared to the fasted state, with an increase in quizartinib Tmax of approximately 2 hours. The t1/2 of quizartinib was comparable with or without food. The slight food effect of Tmax increase is not considered to be clinically relevant and quizartinib can be administered with or without food. An oral dose of quizartinib administered in the fasted state has been chosen in this absolute

bioavailability study, as fasted oral dosing is the standard study design for absolute bioavailability studies. (This is also the route of administration for ongoing clinical studies and the approved route of administration in Japan.)

The primary objective of this study is to determine the absolute oral bioavailability of quizartinib, based on the dose-adjusted exposure of quizartinib following oral and IV administration. Furthermore, characterization of the PK of total radioactivity will be performed to provide additional information on the metabolism of quizartinib, by demonstrating the amount of circulating radioactivity that is not accounted for by the presence of ^{14}C-quizartinib and ^{14}C-AC886. To achieve these objectives, the PK sampling schedule has been selected on the basis of data from previous studies in which single oral doses of quizartinib have been administered to healthy volunteers. The frequent sampling schedule that follows the single doses of quizartinib and ^{14}C-quizartinib is designed to capture data at a sufficient number of time points to provide a detailed profile of the PK of quizartinib and its main metabolite. A 504-hour sample collection period is planned based on the projected total radioactivity recovery of close to 85% based on the previous clinical ADME study AC220-006. Moreover, both quizartinib and AC886 have long terminal elimination half- lives (t1/2) of approximately 73 hours and 119 hours, respectively, and therefore PK sampling until 504 hours post-dose is planned in order to ensure the terminal eliminations phases of both analytes are captured.

The first exploratory objective of this study is to assess the fecal and urinary recovery of total radioactivity following a single, IV administration of 50 µg ^{14}C-quizartinib. In the clinical ADME study AC220-006, the total radioactivity dose recovery observed after 14 days post-dose was <80% and was considered inadequate. Therefore, it is planned to collect urine and fecal samples for up to 504 hours post-dose, as this will enable assessment of the recovery of total radioactivity following an IV dose of ^{14}C-quizartinib over a longer collection period to that previously performed. The fecal and urinary recovery of quizartinib and AC886 following a single, oral dose of 60 mg quizartinib will also be assessed.

Additionally, the whole blood PK of quizartinib and AC886 will be characterized, including the whole blood-to-plasma concentration ratios of both analytes. This is being performed in order to assess clinical blood-to-plasma partitioning, as there is evidence of concentration-dependent blood-to-plasma partitioning occurring in vitro.

An open-label study design is felt to be suitable because quizartinib and ^{14}C-quizartinib concentrations, on which the primary endpoints are based, are objective measures.

4.3. Justification for Dose

The quizartinib dose of 60 mg is the approved dose for relapse/refractory AML in Japan and the maximum maintenance therapeutic dose currently being investigated for AML first-line therapy in the QuANTUM-First study NCT02668653 (7).

This an absolute bioavailability study where an IV microdose of quizartinib containing microtracer amounts of ^{14}C is administered following administration of an oral dose of quizartinib to determine the bioavailability of the oral dose compared with the IV dose. According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3 guidance, a microdose is a dose that is <1/100th of the pharmacologically active dose up to a maximum of 100 µg. In addition, to ensure that the IV

microdose does not contribute significantly to the exposure following oral dosing, the IV dose is reduced further and in this study will be 1/1200th of the oral dose.

The IV microtracer dose has been selected to contain NMT 22.84 kBq. This has been selected as it is below the standard radioactive dose used in this type of study, and will be sufficient to meet the objectives, but contains a low enough amount of radioactivity so as not to cause a significant risk to the subjects.

Therefore the IV dose for this study will be 50 µg ^{14}C-quizartinib containing NMT 22.84 kBq. This IV dose is 1/1200th of the oral dose administered in this study and <1/100th of the likely therapeutic dose, and hence is an appropriate 'IV microtracer dose'.

To ensure that the [^{14}C] drug product does not exceed the limit for radioactive dose approved by ARSAC, the target specific activity of the drug substance will be set at 90% of 90% of the threshold radioactive dosing limit. This will allow for tolerances in the manufacturing processes for both drug substance and drug product thereby providing continued assurance for compliance with the ARSAC-approved limit for drug product radioactivity dose.

5. STUDY POPULATION

This Phase 1 study is being conducted in healthy male subjects.

Subjects will be recruited from the Quotient panel or by direct advertising to the public.

Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not been dosed in a study within 90 days of the planned dosing date of this study.

5.1. Inclusion Criteria

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

1. Healthy males.
2. Aged 18 years to 55 years of age (inclusive) at the time of signing informed consent.
3. Body mass index (BMI) of 18.0 kg/m^2 to 32.0 kg/m^2 (inclusive) at screening.
4. Must be willing and able to communicate and participate in the whole study.
5. Must provide written informed consent.
6. Subjects must agree to use one of the means of contraception specified in Section 5.3 from screening until 115 days after the dose of quizartinib.
7. Subjects must agree to avoid sperm donation for the duration of the study until 115 days after the dose of quizartinib.
8. Subjects must refrain from donation of blood or plasma within the previous 3 months, and platelets within 6 weeks, and must not have loss of greater than 400 mL of blood, throughout the study duration, and for at least 90 days following last dose of study medication.
9. Liver function test results must be below the upper limit of normal (ULN) and hemoglobin levels must be ≥ 12.5 g/dL (125 g/L) at screening and admission (Day -1).
10. Must have regular bowel movements (ie average stool production of ≥1 and ≤3 stools per day)
11. All subjects must be willing to refrain from consuming grapefruit/grapefruit juice, cranberries/cranberry juice, Seville oranges, and pomegranates/pomegranate juice from 10 days before the dose of the study drug is given on Day 1 until discharge from the clinical unit.
12. All subjects must be willing to refrain from consuming anything likely to disturb GI transit (eg spicy or high-fat meals, such as curry or fish and chips, or foods of a high-fiber content such as All Bran) for 24 hours prior to admission (Day -1) until discharge from the clinical unit.
13. All subjects must be willing to refrain from consuming food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to admission (Day -1) until discharge from the clinical unit.
14. All subjects must be willing to refrain from showering for 24 hours post-oral dose (to ensure the collection of all samples).

Inclusion criteria 9, 11, 12, 13, and 14 from the list above will be re-assessed at admission/pre-dose.

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, GI, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, as judged by the Investigator.
   - 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 stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (with the exception of appendectomy, and/or hernia repair, unless it was performed within the previous 12 months).
3. Acute diarrhea or constipation in the 7 days before the predicted Day 1. If screening occurs >7 days before the Day 1, this criterion will be determined at admission/pre-dose. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as a failure to open the bowels more frequently than every other day.
4. History of a clinically significant illness, in the opinion of the Investigator, within 4 weeks prior to administration of quizartinib.
5. Evidence of current SARS-CoV-2 infection.
6. Clinically significant history or presence of acute or chronic bacterial, fungal, or viral infection (eg, pneumonia, septicemia) within the 3 months or 90 days prior to screening or admission (Day -1).
7. Any subject with clinically significant symptoms of COVID-19 in the last 4 weeks, including but not limited to fever, new and persistent cough, breathlessness or loss of taste or smell, as per the judgement of the Investigator.
8. Known or suspected malignancy, autoimmune disorder, or any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status or any factor that would predispose participants to develop infection (eg, open skin lesions, recurrent issues related to poor dentition, perianal fissures, history of splenectomy, primary immunodeficiency).
9. Presence or history of clinically significant allergy requiring treatment, as judged by the Investigator. Hay fever is allowed unless it is active
10. Bradycardia of less than 50 beats per minute.
11. History, or presence in the average of triplicate ECGs at screening and admission (Day -1), of any of the following cardiac conduction abnormalities:
    - QTcF > 450 ms.
    - Evidence of second- or third-degree atrioventricular block.

- Evidence of complete left or right bundle branch block.
- QRS or T wave morphology that could, in the Investigator's opinion, render QT interval assessment unreliable (confirmed with triplicate ECG).

12. Diagnosis or suspicion of long QT syndrome (including family history of long QT syndrome).
13. Presence or history of clinically severe adverse reaction to any drug.
14. 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.
15. History of moderate to heavy alcohol use defined as consumption of more than 21 units of alcohol per week for males, where 1 unit of alcohol equals ½ pint of beer or a 25 mL shot of 40% spirit, and 1.5 to 2 units equal 125 mL glass of wine, depending on type, or significant history of alcoholism or drug/chemical abuse within the last 2 years.
16. A confirmed positive alcohol breath test at screening or admission (Day -1).
17. Loss of more than 400 mL blood during the 3 months before the trial (e.g., as a blood donor).

Physical Examination

18. Subjects who do not have suitable veins for multiple venipunctures/cannulation as assessed by the Investigator or delegate at screening.

Medication Use and Lifestyle

19. Current smokers and those who have smoked within the last 12 months. A confirmed positive urine cotinine test at screening or admission (Day -1).
20. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months.
21. Use of drugs with a risk of QT interval prolongation or TdP within 14 days of admission (Day -1) (or 5 drug half-lives, if 5 drug half-lives are expected to exceed 14 days).
22. 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 admission (Day -1) and during the study.
23. 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 admission (Day -1).
24. Use of any prescribed or over-the-counter (OTC) systemic, herbal (including St John's wort), or topical medication within 14 days of admission (Day -1), or any expectation of requiring use of such medication while participating in the study is prohibited.

    Note: COVID-19 vaccines are accepted concomitant medications. The use of acetaminophen (i.e., paracetamol) of up to 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.

25. Start of any new medication or any changes to a current dosage within 14 days prior to quizartinib administration.
26. Consumption of alcohol- and caffeine-containing beverages within 72 hours prior to admission (Day -1) and during confinement.
27. Engagement in strenuous exercise from the 72 hours before the screening visit and then from 72 hours prior to admission (Day -1) until the discharge from the clinical unit.

Laboratory Tests

28. Laboratory results (serum chemistry, hematology, coagulation, and urinalysis) outside the normal range, if considered clinically significant by the Investigator at screening or admission (Day -1).
29. Estimated creatinine clearance (CrCl) <90 mL/min (calculated using the Cockcroft-Gault Equation equation) at screening.
30. Has a positive serology for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), hepatitis A virus (HAV), or human immunodeficiency virus (HIV) at screening.
31. Has a positive urine screen for drugs of abuse at screening or at admission on Day -1.
32. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1.
33. Subjects who report to have previously received quizartinib.
34. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017 (8), shall participate in the study.
35. Subjects who have been administered IMP in an ADME study in the last 12 months.

Other (Miscellaneous) Exclusions

36. Male subjects with pregnant or lactating partners.
37. Subjects who are, or are immediate family members of, a study site or Sponsor employee.
38. Failure to satisfy the Investigator of fitness to participate for any other reason.

Exclusion criteria 3, 4, 5, 6, 7, 10, 11, 12, 16, 17, 19, 21, 22, 23, 24, 25, 26, 27, 28, 31, 36, and 38 from the list above will be re-assessed at admission/pre-dose.

5.3. Contraception Requirements

Male Subjects

Males must use a condom plus an approved method of highly effective contraception while enrolled in this study, from the time of informed consent until 115 days after last IMP administration. This has been calculated based on 90 days (one cycle of spermatogenesis) plus 5-half-lives of the metabolite AC886. Five half-lives has been calculated as 25 days.

The following methods are acceptable:

- Vasectomized
- A female partner who is not of childbearing potential
- Female partner's use of combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Female partner's use of progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable/implantable
    - intrauterine hormone-releasing system
- Female partner's use of intrauterine device
- Female partner's bilateral tubal occlusion

These contraception requirements are considered to be more conservative than the guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group (9).

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomized males) that might be harmful to sexual partners. Therefore, even if a male is sexually active with a partner of non-childbearing potential they will be required to use a condom from first administration of IMP until 25 days post-final dose. A woman is considered of childbearing potential unless post-menopausal or permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a follicle stimulating hormone result of ≥40 IU/L.

Alternatively, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

5.4. Screening Failures, Re-screening, and Subject Replacement

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (ie subject has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re consented.

Subjects who withdraw or are withdrawn from the study will not be replaced.

6. STUDY TREATMENT(S)

6.1. Study Drug(s) Description

Table 6.1: Study Drug Dosing Information

Study Drug Name	Quizartinib Dihydrochloride Tablets	[^{14}C]-Quizartinib Solution for Infusion 10 µg/mL (NMT 4.6 kBq/mL)
Dosage Formulation	30-mg tablet[a]	50 µg solution for infusion containing NMT 22.84 kBq ^{14}C in 5 mL
Dosage Level(s)[b]	60 mg (2 x 30 mg tablets)	50 µg (NMT 22.84 kBq ^{14}C)
Route of Administration	Oral	IV
Dosing	Single dose	Single dose
Duration	Once	Once as a 15-minute infusion
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	Please refer to the Drug Product Investigational Medicinal Product Dossier for the details of the packaging Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations
Labeling	Bottles will be labeled as required per local and regulatory requirements	This will be labeled as required per local and regulatory requirements

[a] The oral dose will comprise 2 x 30 mg tablets to achieve a single dose of 60 mg quizartinib dihydrochloride.
[b] Quizartinib and ^{14}C-quizartinib doses are expressed as the dihydrochloride salt. The free base (active moiety) equivalent doses of the 60 mg tablets and 50 µg solution for infusion are 53 mg and 44 µg, respectively.

Quizartinib will be supplied by the Sponsor. The labeled ^{14}C-quizartinib solution for infusion will be manufactured by Quotient Sciences.

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 SOP of the site.

The quizartinib and ^{14}C-quizartinib are medicinal products that are un-licensed in the UK and are for use only in the proposed clinical trial.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments will be stored in a secure,

environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

Where Quotient is manufacturing the IMPs, suitability of the manufacturing process will be documented in a Pharmaceutical Development and Control Strategy Report.

The tablets are manufactured, tested and released in accordance with Current Good Manufacturing Practice Regulations and Qualified Person (QP) released for clinical use.

IMPs will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

6.2.2. Administration

Subjects will be allowed water up to 1 hour before the scheduled oral IMP dosing time and will be provided with 240 mL of water at 1 hour post-oral dose. Water will be allowed ad libitum after 1 hour post-oral dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

After the evening meal on Day -1, subjects will be provided with a light snack and then fast from all food and drink (except water) for a minimum of 8 hours on the day prior to oral dosing until approximately 4 hours post-oral dose (i.e., until administration of the IV dose is complete). Lunch will be provided after completion of the IV administration. An evening meal will be provided at approximately 10 hours post-oral dose and an evening snack at approximately 14 hours post-oral dose. On subsequent days, meals will be provided at appropriate times.

The calorie/fat content of meals are not required to be controlled. Subjects will be provided with a standardized menu.

If, for technical reasons, dosing is delayed for more than 2 hours beyond the expected dosing time, subjects will receive 200 mL of an electrolyte drink (eg Lucozade Sport) at the originally scheduled dosing time, or earlier if possible.

If an individual subject has not experienced a bowel movement in any 36 hour period post-dose, fluid intake should be increased and administration of a mild laxative (eg prune juice or a mild stool softener) should be implemented from 24 hours after the dose of quizartinib (see Section 6.8).

Specific details of IMPs, and doses to be administered are provided in Section 6.1 and Section 4.1.3, respectively. Subjects will be dosed on the morning of Day 1.

The exact time of dosing will be decided based on logistics and will be documented in the source.

The oral dose will be administered with a total of 240 mL of water. If required, additional water may be given with the IMP in 50 mL aliquots and will be recorded in the source but will not be classed as a protocol deviation.

4 hours after the oral dose has been administered, the IV dose will be infused over 15 minutes. This infusion will be in the opposite arm being used for PK sampling.

To assess tolerability of the IV administration, dosing will be staggered. The first subject will receive the oral dose at least 30 minutes prior to the second subject. All subsequent dosing will

be staggered by at least 15 minutes. The IV administration will start at 4 hours post-oral dosing for all subjects, and will therefore be staggered as well.

To allow for potential interruptions and pump variations, up to a 20% difference in duration of the IV infusion will not be considered a protocol deviation provided that full planned dosed is administered as these minor discrepancies should not have a significant impact on the overall study objectives.

The planned infusion time will be 15 minutes; the actual infusion start and stop time will be recorded in the source.

- The infusion will finish within ± 3 minutes of the nominal time point

6.2.3. Storage

Quizartinib dihydrochloride tablets must be stored according to the directions on the label (store up to 25°C [77°F]; do not freeze). The ^{14}C-quizartinib Solution for Infusion must be stored according to the directions on the label.

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

This is an open-label, non-randomized study; therefore, a randomization schedule will not be produced. A treatment allocation will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The treatment allocation will be retained in the ISF.

Subject numbers will be allocated on the morning of dosing according to the code 10011001 to 10011008 using the lowest number available (see also Section 10.1.7.3).

6.3.2. Blinding

This is an open-label study and therefore blinding is not required.

6.4. Treatment Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration. Each dose of the study drugs will be administered by qualified study site staff.

Mouth and hand checks will be conducted after oral dosing to ensure the tablets have been swallowed.

The IV dose will be administered by trained staff to ensure dosing compliance.

The date and time that each subject is dosed will be recorded in the subject's source data. Any violation of compliance will require evaluation by the Investigator and Sponsor to determine if the subject can continue in the study.

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 informed consent form (ICF) for study participation to discharge from the clinical unit will be recorded as concomitant therapies. Concomitant therapies include all prescription, OTC, and herbal remedies.

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

6.7. Prohibited Therapies/Products

Subjects will be prohibited from starting any new medication or undergoing any changes to a current dosage within 14 days prior to quizartinib administration.

Any drugs or substances known to be inhibitors or inducers of CYP3A4/5 (see Section 10.3.2) are prohibited within 28 days from the first dose or 5 half-lives, if known, of the drugs or substances, whichever is greater, prior to admission (Day -1) and during the study.

Additionally, 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 admission (Day -1) and throughout the study:

- Drugs with a risk of QT interval prolongation or TdP
- Medications known to affect the elimination of serum creatinine (e.g., trimethoprim or cimetidine) and inhibitors of renal tubular secretion (e.g., probenecid)
- Any prescribed or OTC systemic, herbal (including St John's wort), or topical medication, with the exception of those specified in Section 6.6.
- 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 admission (Day -1). However, all dietary supplements are prohibited starting on admission (Day -1) and throughout the study.
- Blood oranges, grapefruit, grapefruit juice, cranberries, cranberry juice, pomegranates, pomegranate juice, Seville (bitter) oranges, and star fruit are prohibited for 10 days before admission (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 admission (Day -1) and throughout the study.
- Beverages, or foods likely to disturb GI transit (eg spicy or high-fat meals, such as curry or fish and chips, or foods of a high-fiber content such as All Bran) are prohibited for 24 hours prior to admission (Day -1) until discharge from the clinical unit.
- Foods containing poppy seeds are prohibited for 48 hours prior to screening and for 48 hours prior to admission (Day -1) until discharge from the clinical unit.

6.8. Permitted Therapies/Products

The use of acetaminophen (i.e., paracetamol) of up to 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.

COVID-19 vaccines are accepted concomitant medications. It is preferable for subjects not to receive the vaccine within 72 hours prior to study drug dosing, where possible, so that by the time of dosing any effects of the vaccine (e.g., pyrexia, fatigue, pain/stiffness at site of injection) are likely to have abated; however, subjects would not be excluded on this basis.

7. WITHDRAWAL/DISCONTINUATION FROM THE STUDY

7.1. Subject Withdrawal/Discontinuation from the Study Drugs

This is a single dose study, therefore, after an individual subject has received a dose of IMP, withdrawal of that subject from further dosing is not possible. Subjects may discontinue from the study for any of the following reasons:

- Adverse event
- Withdrawal by subject
- Investigator decision
- Protocol deviation
- Study termination by Sponsor
- Other

Subjects will be monitored for the following criteria which may require their withdrawal from some or all study procedures if continuation is not in their best interests, except when the withdrawal is a result of withdrawal of consent:

- Experiencing a serious or severe AE including but not limited to:
    - QTcF of >500 ms or increase in QTcF interval of >60 ms from baseline (confirmed following a repeat ECG)
    - ALT concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Termination of the study
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness that would adversely affect subject safety or data integrity or requirement for prohibited medication
- Evidence of current SARS-CoV-2 infection

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (ie a SAE considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (ie severe non-serious AE considered as, at least possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system organ class.

Relatedness to IMP will be determined by the Investigator.

If the study is halted, a temporary halt will be submitted to the MHRA and EC in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be

resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

The ARSAC Practitioner will also be informed of the temporary halt.

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 the Schedule of Events (SoE; Table 1.1) for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

Subjects will be considered lost to follow-up if they leave the CRU prior to discharge from the clinical unit 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 (eg three telephone calls on three separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented.

8. STUDY PROCEDURES

See the SoE, Table 1.1, for the procedures conducted at specific time points during screening, the Treatment Period, and discharge from the clinical unit.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 21 days, all or part of the screening procedures will be repeated at the discretion of the Investigator.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances the following will apply to post-dose time points:

- PK samples should take priority over other procedures scheduled at the same time point
- ECGs should be taken prior to vital signs when both measurements are scheduled at the same time point
- Other assessments, eg physical examinations, will be performed within the required time windows

As guidance, the preferred order of assessments is:

ECGs → **Vitals** → **PK blood sampling (nominal time)** → **Other assessments eg physical examinations**

All assessments will be timed and performed relative to the start of oral dosing.

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, ECG, and laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2).

Screening and admission/pre-dose safety procedures such as safety bloods, ECGs, vital signs, urine drug and cotinine screens, alcohol breath tests and urinalysis can be repeated as clinically indicated under the discretion of the Investigator or Sub-Investigator if there is a concern regarding a subject’s safety or eligibility to participate in the trial.

Reserve subjects for the first dose occasion will not require admission procedures to be repeated, if dosing is within 2 days.

The subjects will be admitted to the clinical unit on the morning before dosing (Day -1).

In addition, subjects may be required to visit the clinical unit on the day before admission for SARS-CoV-2 antigen tests (see Sections 2.3.3.1 and 8.6.3.3). Test results must be available prior to dosing; if test results are delayed, admission procedures are not required to be repeated if dosing is within 2 days.

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 10.1.5 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) Assessments

Pharmacokinetic blood (via an indwelling cannula or by venipuncture), urine and fecal samples will be collected, processed, and shipped as detailed in the SoE and in the Laboratory Processing Specifications as detailed in the Clinical Sample Processing Manual (CSPM; see Section 10.5).

The total blood volume for each subject will not exceed 550 mL in a 4-week period. The first 0.5 mL of blood withdrawn via cannula will be discarded.

Allowable time windows for PK 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 and whole blood quizartinib, plasma and whole blood AC886, plasma ^{14}C-quizartinib, plasma ^{14}C-AC886 and plasma total radioactivity concentrations. Additionally, exploratory metabolite analyses may be conducted using the leftover samples after quizartinib and AC886 analysis and reported separately from the clinical study report for this protocol.

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 PCR or antibody test for COVID-19 is available should be reported as "Suspected COVID-19", either as an AE or SAE.

The usual protocol-mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, i.e., the Investigator should

assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.

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

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

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

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

- Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the laboratory eCRF, if available.
- Clinical course of the case, including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID-19, and outcome in relevant eCRF (e.g., concomitant medication, 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 Adverse Events of Special Interest and Serious Adverse Events

For all enrolled subjects, all AEs occurring after the subject signs the ICF and to discharge from the clinical unit (i.e., Day 22), whether observed by the Investigator or reported by the subject, will be recorded as detailed in Section 10.1.7.2. Additionally, if a subject reports any AEs between discharge and 7 days post-discharge (i.e., between Day 22 and Day 29), they will also be recorded as detailed in Section 10.1.7.2. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. SAEs considered related to the IMP by the Investigator should be reported regardless of the time after the last dose of IMP they occurred.

8.6.2.3. Reporting Procedure for Investigators

All AEs (including adverse events of special interest [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 on a Serious AdVerse Event Report (SAVER) form within 24 hours of awareness to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV) at CSPV-clinical@dsi.com:

- 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.

Contact the Medical Monitor (see Section 10.1.1) 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 Site and Regulatory Authorities

Daiichi Sankyo and/or the CRO will inform Investigator(s) and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or the CRO will comply with any additional local safety reporting requirements.

The Sponsor will comply with any additional local safety reporting requirements. The Sponsor will report SUSARs to all Central ECs, whereas this responsibility can be delegated to the Investigator to inform the local EC. The Sponsor will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB (3).

AEs considered by the Investigator to be related to COVID-19 vaccines will be reported to the MHRA via the Yellow Card system.

All confirmed or suspected COVID-19 vaccine-related events must be recorded in the eCRF.

The usual protocol-mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 vaccine-related AE 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 suspected COVID-19 vaccine-related AE does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious AE in the eCRF.

When assessing the severity of the suspected COVID-19 vaccine-related 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 suspected COVID-19 vaccine-related AE must be recorded on the AE and drug administration eCRFs.

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.

If a subject reports any AEs between discharge and 7 days post-discharge (i.e., between Day 22 and Day 29) that represent a cause for concern, they will be required to attend the clinical unit for a follow-up assessment as per the discretion of the Investigator or delegate. This will be an unscheduled visit.

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

Monitoring in subjects with QTcF prolongation will include the following:

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

8.6.2.8. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to the Sponsor within 24 hours of awareness and recorded via the Serious AdVerse Event Report (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 male subject's female partner that occurs while the subject is receiving or within 115 days 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 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 partner of a male subject, the Exposure In Utero (EIU) Reporting Form (or SAE form if associated with an adverse outcome) should be completed with the subject number, subjects' initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

8.6.3. Clinical Laboratory Evaluations

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

The clinical laboratory tests will include hematology, coagulation, serum chemistry, and urinalysis. Refer to Section 10.2 for the complete list of laboratory parameters.

Allowable time windows for clinical laboratory tests are provided in Section 10.7.

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.

8.6.3.1. Drug Screen

A urine drug and cotinine screen will be performed on-site using a point of care testing method (eg Alere Drug Screen Test Cup) as detailed in the SoE in Section 1.3. The sample will be collected and processed as detailed in the CSPM. Subjects will be screened for the drugs of abuse listed in Section 10.2.

8.6.3.2. Alcohol Breath Test

An alcohol breath test will be performed as detailed in the SoE in Section 1.3. A positive result will exclude the subject from dosing during that admission.

8.6.3.3. SARS-CoV-2 Tests

Testing for the SARS-CoV-2 virus will be performed based on current infection rates and availability of tests. Tests will be performed as detailed in the SoE in Section 1.3. The samples will be collected and processed as detailed in the Screening Sample Processing Manual and CSPM.

Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points

will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.

8.6.4. Body Weight, Height and BMI

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

8.6.5. Physical Examinations

Physical examinations will be performed as detailed in the SoE 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, GI, and neurological systems.

In the targeted (symptom driven) physical examination, a physician will assess the subject; if the subject reports feeling unwell or has ongoing AEs, then the physician will examine the appropriate body system(s) if required.

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.

8.6.6. Vital Signs

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

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

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

8.6.7. Electrocardiograms

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

Allowable time windows for ECGs are provided in Section 10.7.

Triplicate 12-lead ECGs (approximately 2 minutes apart) will be 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 in triplicate. 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 mandatory single blood sample for pharmacogenomic (PGx) analysis will be collected pre-dose from each enrolled subject. Detailed instructions for the collection, handling, and

shipping of samples are outlined in the Laboratory Specifications Document as detailed in the CSPM.

Genetic analyses will not be performed on blood samples collected for PK or safety assessments. Subject confidentiality will be maintained; data will be decoded and the testing lab will not have traceability information.

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

8.7.1. Banking of Specimens for Inherited Genetic Analysis

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

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 (at Thermo Fisher Scientific, United States of America [USA] or other provider selected by the Sponsor) 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.

The samples will be destroyed in line with Thermo Fisher Scientific's/the provider's SOPs and in line with local regulations.

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 calculations. 8 subjects will be enrolled in the study to target at least 6 subjects to complete the PK evaluation (i.e., to allow for withdrawal or non-PK evaluability in up to 2 dosed subjects).

9.3. Exposure and Compliance

As the dose administration is under the control of the study site, 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 Population is defined as all subjects who received the study drug and have a corresponding measurable concentration. The PK Analysis Population will be used for the descriptive statistics of concentration data and to generate mean and individual concentration time profiles.

The PK Evaluable Population includes all subjects who are evaluable as defined below and have a sufficient number of measurable concentrations to estimate PK parameters. An evaluable subject is defined as a subject who has received both the oral and IV microtracer IMPs (i.e., a single, oral dose of 60 mg quizartinib dihydrochloride tablets [2 x 30 mg tablets] and an IV administration of 50 µg 14C-quizartinib solution for infusion 10 µg/mL containing NMT 22.84 kBq 14C in 5 mL [NMT 4.6 kBq/mL] over 15 minutes at 4 hours post-oral dose) and has sufficient samples for evaluation of plasma PK parameters. The PK Evaluable Population will be used for summaries of PK parameter estimates.

Additional exclusions and flags may be required to address relevant protocol deviations and AEs.

Specific exclusions may be made for the fecal and urine datasets in relation to missing and/spilled samples.

9.4.2. Safety Population

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

9.5. Statistical Analysis

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for

missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

No formal interim analyses are planned for this study.

9.5.1. Safety Analysis

9.5.1.1. Adverse Events

Treatment-emergent adverse events are defined as new AEs that occur after the first dose of study drug. AEs occurring after Day 29 will not be considered TEAEs unless they are treatment-related. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (see Section 10.1.7.3). An AE will be assigned to the study day on which it started, even if it resolved on a subsequent day. The incidence of TEAEs will be summarized. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, and by preferred term.

Treatment-emergent adverse events, or AEs that are present prior to the first dose but which worsen in severity after the first dose of study drug, will be further summarized by common terminology criteria for adverse events (CTCAE) grade and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and related treatment-emergent SAEs will be tabulated, treatment-emergent AESIs, and TEAEs leading to discontinuation of study drug.

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

9.5.1.2. Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation, 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 for the maximum and minimum post-treatment values and the values at discharge from the clinical unit.

Abnormal clinical laboratory results will be appraised by the site physician where any results of clinical significance will be recorded as an AE, and graded according to National Cancer Institute - common terminology criteria for adverse events (NCI-CTCAE) Version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting 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 Grade 3 or 4 results will be generated.

9.5.1.3. Electrocardiograms

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation, 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; changes from baseline of ≥30 ms to <60 ms, and ≥60 ms).

A listing of ECG data will be generated.

9.5.1.4. Vital Signs

Descriptive statistics will be provided for the vital sign measurements by scheduled time of evaluation, 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 signs data will be generated.

9.5.1.5. Other

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

9.5.2. Pharmacokinetics Analysis

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

9.5.2.1. Pharmacokinetic Parameters

Pharmacokinetic and statistical analysis will be performed using appropriate software; e.g., Phoenix™ WinNonlin® (Version 8.0 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 approach.

The following PK parameters will be calculated for plasma and whole blood quizartinib, plasma and whole blood AC886, plasma ^{14}C-quizartinib, plasma ^{14}C-AC886 and plasma total radioactivity, as applicable.

Cmax	The maximum observed concentration
Tmax	Time to reach maximum observed concentration
Kel	First order rate constant associated with the terminal portion of the concentration-time curve. This is estimated via linear regression of time vs log concentration.
t1/2	Terminal half-life
AUClast	AUC from the time of dosing to time Tlast
AUCinf	AUC from the time of dosing extrapolated to infinity
AUCextr (%)	Percentage of AUCinf that is due to extrapolation from Tlast to infinity 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 observed concentration
Tlast	Time of the last measurable (non-zero) concentration

CL	Total body clearance following single-dose iv administration (for plasma ^{14}C-quizartinib only)
CL/F	Apparent total body clearance following single-dose extravascular administration (for plasma and whole blood quizartinib only)
Vz	Volume of distribution based on the terminal phase following a single-dose of iv administration (for plasma ^{14}C-quizartinib only)
Vz/F	Apparent volume of distribution based on the terminal phase following a single-dose of extravascular administration (for plasma and whole blood quizartinib only)
MPR Cmax	Metabolite-to-parent ratio for Cmax (for plasma and whole blood AC886 and plasma ^{14}C-AC886 only)
MPR AUClast	Metabolite-to-parent ratio for AUClast (for plasma and whole blood AC886 and plasma ^{14}C-AC886 only)
MPR AUCinf	Metabolite-to-parent ratio for AUCinf (for plasma and whole blood AC886 and plasma ^{14}C-AC886 only)
F	The fraction of the administered dose systemically available
Kbp	Whole blood-to-plasma concentration ratio

The following PK parameters will be calculated for total radioactivity quizartinib and AC886 in urine and feces by discrete collection interval and cumulatively as applicable.

Ae(t1-t2)	Amount of total radioactivity, quizartinib and AC886 excreted in urine/feces from time t1 to time t2 for each collection interval
Fe(t1-t2)	Amount of total radioactivity, quizartinib and AC886 excreted in urine/feces expressed as a percentage of the IV (total radioactivity) or oral (quizartinib and AC886) dose administered from time t1 to time t2 for each collection interval

9.5.2.2. Statistical Analysis of Pharmacokinetic Endpoints

The PK Analysis Population and the PK Evaluable Population will be used for PK analyses, details of which will be presented in the SAP.

Using the PK Analysis Population, descriptive statistics will be presented for plasma and whole blood concentrations at each sampling time point. Plasma concentration-time data will be analyzed using non-compartmental methods. Whole blood-to-plasma quizartinib and AC886 concentration ratios (Kbp) will also be calculated at each sampling time point.

The PK Evaluable Population will be used for the calculation and summaries of the PK parameters listed in Section 9.5.2.1.

Note that when percent extrapolated AUC (AUCextr (%)) is greater than 20%, AUCinf and related parameters will be summarized with and without those individuals having >20% AUCextr (%). For the primary analysis, including calculation of absolute bioavailability (F), individuals having >20% AUCextr (%) will be excluded. An additional subset may be required in order to include individuals having >20% AUCextr (%); this will be documented in the clinical study report.

Absolute bioavailability (F) will be calculated based on the dose-normalized quizartinib plasma AUCinf after the oral dose (data from the cold assay [i.e., ^{12}C-quizartinib] will be used for this analysis) to the dose-normalized AUCinf after the IV dose (data from the hot assay [i.e., ^{14}C-quizartinib] will be used for this analysis).

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the IB, available safety information, recruitment procedures (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 EC 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 substantial protocol amendments and changes to any of the above listed documents must be obtained from the EC and other local regulatory authorities.

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

The contact information for the Sponsor's PPD who must be contacted first, is as follows:

Name, qualifications: PPD

Telephone No. (Mobile): PPD

Email address: PPD

The contact information for the Sponsor's PPD is as follows:

Name, qualifications: PPD

Telephone No.: PPD

Email address: PPD

The contact information for Quotient's PPD is as follows:

Name, qualifications: PPD

Telephone No.: PPD

Email address: PPD

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 ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US 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 the Investigator becomes aware.

10.1.3. Administration of Radiation

Administration will be conducted in accordance with PPD current PPD license and Quotient Sciences' current ARSAC Employer license. Additionally a research application will be submitted to ARSAC to obtain approval for the conduct of the study before dosing.

The protocol will be reviewed and the final version will be approved by the ARSAC practitioner, PPD

10.1.4. 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 EC, 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 EC. 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.

10.1.5. 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 EC 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.

10.1.6. 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 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.

10.1.7. Data Integrity and Quality Assurance

10.1.7.1. 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.

10.1.7.2. Data Collection

An eCRF must be completed for each enrolled subject. Screen failure information will be collected at the clinical site in a log. All data collected for enrolled 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 electronic data capture (EDC) system's electronic signature. This signature will indicate that the Investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

10.1.7.3. Data Management

Each subject will be identified in the database by a unique subject identifier PPD

To ensure the quality of clinical data across all subjects, a data management review will be performed on subject data according to specifications developed by the Sponsor. These processes will be performed according to the Data Management Plan.

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 and Medical Histories will be coded using MedDRA (Version 23.1 or a more recent version). Medications will be coded using the World Health Organization (WHO) Drug Dictionary Global Drug Reference (Sep 2020 or a more recent version). Serious adverse events in the clinical database will be reconciled with the safety database.

10.1.7.4. 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, EC 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.

10.1.7.5. Record Keeping

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

Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent EC 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.

10.1.8. 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.

10.1.9. 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.

10.1.10. Publication and Public Disclosure Policy

10.1.11. 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 ECs.

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 major 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 EC of deviations from the protocol in accordance with local procedures.

10.1.12. Study and Site Closure

The Sponsor reserves the right to close the study site and terminate the study at any time for any reason at the sole discretion of the Sponsor. The study site 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 EC 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.

10.1.13. 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 Sponsor’s SOPs for instructions and details.

10.1.14. Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines (10), each subject will receive a card stating the telephone number of the Investigator and the 24/7 contact details of the Quotient's on-call physician.

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 by The Doctors Laboratory (The Halo Building, 1 Mabledon Place, London WC1H 9AX; Tel: + 44 [0]207 3077 404).

Venous blood and urine samples will be collected from the subjects by a trained member of the clinical team. Subjects will sign a study-specific ICF, in which they will consent to the use of these samples for the purposes of the proposed study.

Blood and urine samples are sent for laboratory testing and are identified by the study number, the subject's volunteer panel number, sample type, date of sample, and the subject's gender and date of birth (for analytical reasons). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor; however, not by the laboratory staff or Sponsor.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse and cotinine tests and urinalysis will be carried out on urine samples.

Blood and urine samples will be processed as described in the CSPM.

Safety blood and urine samples results will be reviewed by a physician and acted upon before the subject is dosed or receives their next dose, or is released from the study, as is appropriate.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Serum Chemistry	albumin albumin globulin (A/G) ratio alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bicarbonate/CO2 bilirubin (total) bilirubin (direct) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine cholesterol (total)	creatine phosphokinase gamma-glutamyl transaminase (GGT) glucose ([non-fasting/fasting]) lactate dehydrogenase lipase lipoprotein, high density (HDL) lipoprotein, low density (LDL; note: LDL value is calculated) magnesium (Mg) phosphorus potassium (K) protein (total) sodium (Na) triglycerides 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	Activated partial thromboplastin time (aPTT)/prothrombin time (PT)/international normalized ratio (INR)	
Urinalysis (abbreviated)	bilirubin glucose ketone bodies occult blood pH protein specific gravity nitrites	urobilinogen sediments: casts RBC WBC Microbiology and/or urine microscopy (at discretion of Investigator based on urinalysis results)
Virology	Hepatitis B Surface Antigen (HBsAg) Hepatitis C Virus Antibody (HCV) Human Immunodeficiency Virus (HIV) Antibody Hepatitis A Virus (HAV)	SARS-CoV-2 Antibody (if required) SARS-CoV-2 Antigen (if required)
Drugs of abuse	Amphetamines Barbiturates Benzodiazepines Cocaine Marijuana/Cannabis Methadone	Methamphetamine/ecstasy Morphine/Opiates Phencyclidine Tricyclic Antidepressants Cotinine

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

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

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

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)} \times 1.23}{\text{serum creatinine (in µmol/L)}}$$

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, coagulation, serum chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, which require investigation or corrective measures, or are 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 SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

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

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (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 AE and the study drug based on his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (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 will be categorized as follows:

- Quizartinib when administered alone (from 0 to 4 hours post-oral dose)
- Quizartinib and ^{14}C-quizartinib (after the start of IV administration at 4 hours post-oral dose)

10.4.6. Action Taken Regarding Study Drug(s)

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

10.4.7. Other Action Taken for Event

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

10.4.8. Adverse Event Outcome

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

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

Details of pharmacokinetic blood, urine and fecal samples collection, processing, storage, and shipment will be contained in the CSPM.

Venous blood samples will be collected from the subjects by a trained member of the clinical team. Subjects will sign a study-specific ICF, in which they will consent to the use of these samples for the purposes of the proposed study. Samples will be processed to isolate plasma and PK analysis will be carried out on plasma samples.

Plasma, whole blood, urine and fecal samples will be sent for laboratory testing in linked anonymized form (identified by identified by the study number, subject's volunteer panel number/subject number, date of sample and time point of blood draw). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor, however not by the laboratory staff or Sponsor.

The pre-dose urine sample will be taken any time between admission and pre-dose. Where a sample is not provided, this will not be considered a deviation.

The pre-dose fecal sample will be taken any time between admission and pre-dose. If a pre dose fecal sample cannot be obtained, the subject will still be dosed. Where a sample is not provided, this will not be considered a deviation.

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

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

Details of PGx blood samples collection, processing, storage, and shipment will be contained in the CSPM.

10.7. Appendix 7: Allowable Time Windows for Pharmacokinetic Blood, Urine and Fecal Samples, Clinical Laboratory Safety Samples, and Vital Sign, and Electrocardiogram Assessments

Table 10.4: Acceptable Time Windows

Procedures (in order of collection)	**Allowable Time Window**	
	Pre-dose	**Post-dose**
ECG (pre-dose, 4, 24, 72 and 504 hours post-oral dose)	No more than **2** hours before oral dose; inclusive of at least 5 minutes of quiet rest in the supine position	No more than ± **15** minutes from the nominal post-dose time point (4 through 72 hours post-oral dose); inclusive of at least 5 minutes of quiet rest in the supine position
		No more than ± **1** hour from the nominal post-dose time point (504 hours post-oral dose [discharge]); inclusive of at least 5 minutes of supine rest
	Approximately **2** minutes between triplicate ECGs (i.e. **1** to **3** minutes allowed between each of the triplicate ECGs)	Approximately **2** minutes between triplicate ECGs (i.e. **1** to **3** minutes allowed between each of the triplicate ECGs)
Vital signs (pre-dose, 4, 24, 72 and 504 hours post-oral dose)	No more than **2** hours before oral dose; inclusive of at least 5 minutes of supine rest	No more than ± **15** minutes from the nominal post-dose time point (4 through 72 hours post-oral dose); inclusive of at least 5 minutes of supine rest
		No more than ± **1** hour from the nominal post-dose time point (504 hours post-oral dose [discharge]); inclusive of at least 5 minutes of supine rest
Hematology, Serum Chemistry (96 and 504 hours post-oral dose)	Not applicable	No more than ± **1** hour from the nominal post-dose time point
Coagulation (pre-dose, 96, and 504 hours post-oral dose	No more than **2** hours before oral dose	No more than ± **1** hour from the nominal post-dose time point
Urinalysis (96 and 504 hours post-oral dose)	Not applicable	No more than ± **2** hours from the nominal post-dose time point

PK blood sample collection (pre-dose, 1, 2, 4, 4.25, 4.5, 4.75, 5, 6, 8, 12, 24, 48, 72, 96, 144, 192, 240, 288, 336, 384, 432, 480, and 504 hours post-oral quizartinib dose)	No more than 60 minutes before dosing (applies to all pre-dose PK blood samples, including the pre-dose plasma PK samples for total radioactivity, ^{14}C-quizartinib and ^{14}C-AC886 that are to be taken prior to the start of the IV infusion)	No more than ± **2** minutes from the nominal post-dose time point (1 through 5 hours post-oral dose)
		No more than ±1**0** minutes from the nominal post-dose time point (6 through 12 hours post-oral dose)
		No more than ±**30** minutes from the nominal post-dose time point (24 through 504 hours post-oral dose)
PK urine sample collection (pre-dose, 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours post-oral dose and then daily [24 hour intervals] until discharge at 504 hours post-oral dose [Day 22])	Any time between admission and pre-dose	Nominal time window to be observed
PK fecal sample collection (pre-dose and 24 hour intervals post-oral dosing until discharge [Day 22])	Any time between admission and pre-dose	Nominal time window to be observed

11. REFERENCES

1. FDA Guidance: Food effect bioavailability and fed bioequivalence studies. 2002.
2. EMA – Guidance on the investigation of bioequivalence. 20 Jan 2010.
3. Quizartinib (AC220) Investigator's Brochure. Edition 15.0. 29 Jan 2021.
4. Davies NG, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020; 26(8): 1205–1211.
5. Li H, et al. Age-dependent risks of incidence and mortality of COVID-19 in Hubei Province and other parts of China. Front Med (Lausanne). 2020; 7: 190.
6. Liu Y, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020; 55: 2001112.
7. 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.
8. Health and Safety. Ionising Radiation (Medical Exposure) Regulations 2017. Statutory Instrument 2017 No. 1322.
9. Heads of Medicines Agency: Clinical Trials Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. 15 Sep 2014 http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.
10. Guidelines for Phase I Clinical Trials. Association of the British Pharmaceutical Industry Guidelines. London, UK; 2018 Edition (publication date 29 May 2018).

12. LIST OF ABBREVIATIONS

Abbreviation	Definition
^{14}C	carbon-14
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
Ae(t1-t2)	Amount excreted in urine/feces from time t1 to time t2 for each collection interval
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AMS	accelerator mass spectrometry
aPTT	activated partial thromboplastin time
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	aspartate aminotransferase
AUC	area under the curve
AUCextr (%)	Percentage of AUCinf that is due to extrapolation from Tlast to infinity
AUCinf	AUC from the time of dosing extrapolated to infinity
AUClast	AUC from the time of dosing to time Tlast
BMI	body mass index
CFR	Code of Federal Regulations
CL	Total body clearance following single-dose iv administration
Clast	The last observed concentration
CL/F	Apparent total body clearance following single-dose extravascular administration
Cmax	The maximum observed concentration
COVID-19	coronavirus disease 2019
C QTc	concentration-corrected QT interval
CrCl	creatinine clearance
CRU	clinical research unit
CRO	contract research organization
CSPM	Clinical Sample Processing Manual
CSPV	Clinical Safety and Pharmacovigilance
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450

Abbreviation	Definition
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ET	early termination
EIU	Exposure In Utero
EU	European Union
F	The fraction of the administered dose systemically available
FDA	Food and Drug Administration
Fe(t1-t2)	Amount excreted in urine/feces expressed as a percentage of the dose administered from time t1 to time t2 for each collection interval
FLT3	Feline McDonough sarcoma-like tyrosine kinase 3
FMS	Feline McDonough sarcoma
GCP	Good Clinical Practice
GPP3	Good Publication Practice for Communicating Company-Sponsored Medical Research
GI	gastrointestinal
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
HI	hepatic impairment
HIV	human immunodeficiency virus
HPLC MS/MS	high-performance liquid chromatography mass spectrometry/mass spectrometry
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
ICMJE	International Council of Medical Journal Editors
IMP	investigational medicinal product
INR	international normalized ratio
ISF	Investigator Site File

Abbreviation	Definition
ITD	internal tandem duplication
IUD	intrauterine device
IV	intravenous
Kel	First order rate constant associated with the terminal portion of the concentration-time curve. This is estimated via linear regression of time vs log concentration.
KIT	KIT proto oncogene receptor tyrosine kinase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MPR	metabolite-to-parent ratio
MPR AUCinf	Metabolite-to-parent ratio for AUCinf
MPR AUClast	Metabolite-to-parent ratio for AUClast
MPR Cmax	Metabolite-to-parent ratio for Cmax
NCI-CTCAE	National Cancer Institute - common terminology criteria for adverse events
NMT	not more than
NRU	neutral red uptake
OTC	over-the-counter
PCR	polymerase chain reaction
PGx	pharmacogenomic(s)
PHE	Public Health England
PK	pharmacokinetic
PT	prothrombin time
QP	Qualified Person
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAVER	Serious AdVerse Event Report
SI	International System of Units
SoE	Schedule of Events
SOP	standard operating procedure

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
t1/2	Terminal half-life
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
Tlast	Time of the last measurable (non-zero) concentration
Tmax	Time to reach maximum observed concentration
TOPS	The Over Volunteering Prevention System
ULN	upper limit of normal
UK	United Kingdom
US	United States
USA	United States of America
Vz	Volume of distribution based on the terminal phase following a single-dose of iv administration
Vz/F	Apparent volume of distribution based on the terminal phase following a single-dose of extravascular administration
WHO	World Health Organization