Clinical Study Protocol

A Phase 2 Open-label, Single-arm Study of Quizartinib (AC220) Monotherapy in Japanese Patients with FLT3-ITD Positive Refractory or Relapsed Acute Myeloid Leukemia

AC220-A-J201

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Daiichi Sankyo Co., Ltd.

PROTOCOL SYNOPSIS

Protocol number:	AC220-A-J201
Investigational product:	Quizartinib
Active ingredient/ r-INN:	AC220/quizartinib
Study title:	A Phase 2 Open-label, Single-arm Study of Quizartinib (AC220) Monotherapy in Japanese Patients with FLT3-ITD Positive Refractory or Relapsed Acute Myeloid Leukemia
Phase of development:	Phase 2
Indication under investigation:	Acute myeloid leukemia (AML)
Study objectives:	<Primary objective> To evaluate the composite complete remission (CRc) rate (defined as the proportion of patients whose best response is complete remission [CR], CR with incomplete platelet recovery [CRp], or CR with incomplete hematological recovery [CRi]) after treatment with quizartinib as multiple-dose monotherapy in Japanese patients with FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive relapsed or refractory AML. <Secondary objectives> • To evaluate the best response with quizartinib • To evaluate the response rate with quizartinib • To evaluate the overall survival with quizartinib • To evaluate the event-free survival with quizartinib • To evaluate the leukemia-free survival with quizartinib • To evaluate the transplantation rate with quizartinib • To evaluate the safety of quizartinib • To evaluate the pharmacokinetics of quizartinib • To evaluate quizartinib-related biomarkers

	<Type of study objectives> Efficacy, safety, and pharmacokinetics
Study design:	Type of study: Interventional Type of intervention: Pharmaceutical drugs Type of proposed indications: Treatment Study design: Single arm (two-stage design) <Stage 1> Concerning the 25 patients included in the efficacy analysis set, the study will be terminated both if CR, CRp, or CRi (CRc) is achieved in 3 or fewer patients (the treatment will be determined to be ineffective), or if CR, CRp, or CRi (CRc) is achieved in 11 or more patients (the treatment will be determined to be effective). Meanwhile, if CRc is achieved in 4 to 10 patients, registration of patients will be continued until 41 patients are included in the efficacy analysis set (addition of 16 patients in Stage 2). <Stage 2> Concerning the 41 patients included in the efficacy analysis set, if CRc is achieved in 15 or more patients, the treatment is determined to be effective (rejection of the null hypothesis). Level of blinding: Open-label Type and presence/absence of comparator: Not applicable Presence/absence of add-on to standard therapy: Not applicable
Planned study period:	01 Dec 2016 to 31 Mar 2019
Study centers and location:	Refer to Attachment 1.
Subject eligibility criteria:	1) Provision of written informed consent for participation in the study. 2) Patients aged 20 years or older when consent is obtained. 3) Primary AML patients or AML patients with a history of myelodysplastic syndrome (MDS). 4) AML patients who have first relapsed within 6 months after achieving remission with initial remission induction

therapy or those who are refractory to all therapies given prior to the start of the study and failed to achieve remission. The initial remission induction therapy must be a regimen containing at least 1 cycle of standard-dose treatment with anthracyclines or mitoxantrone. It is not taken into consideration whether they have hematopoietic stem cell transplant (HSCT) or not.

- Definition of refractory to treatment
  - Patients who have less than 50% reduction in bone marrow blasts and have failed to achieve CR, CRp, or CRi after 1 cycle of treatment.
  - Patients who have failed to achieve CR, CRp, or CRi after 2 cycles of treatment.
- Definition of first relapse (within 6 months after achieving remission)
  - Patients who have achieved CR, CRp, or CRi after initial remission induction therapy and have relapsed within 6 months. It is not taken into consideration whether they have received consolidation therapy, maintenance therapy, or HSCT or not.
  - The duration of remission is defined as the day of the bone marrow test when CR, CRp, or CRi was confirmed or the day of HSCT to the day of the bone marrow test when relapse was confirmed or the day of reappearance of leukemic blasts in the peripheral blood.

5) Patients with mutations of the FLT3-ITD gene in bone marrow or peripheral blood.
   * A specimen for the FLT3-ITD mutation test will be submitted to Navigate BioPharma Services, Inc. (Navigate BioPharma), the central laboratory, to test mutations in the FLT3-ITD gene. However, patients who have been confirmed to be FLT3-ITD positive in the FLT3-ITD testing previously performed at another testing company or

the central laboratory, SRL Inc., may be assessed for eligibility for the study without waiting for the result of measurement at Navigate BioPharma.

6) Eastern Cooperative Oncology Group performance status (ECOG PS) score 0 to 2 (refer to "Appendix 2").
7) Patients in whom the intervals listed below can be achieved between the last dose or application of prior therapy and the first dose of the study drug in the study:
   - Cytotoxic drugs (excluding hydroxycarbamide used for the purpose of controlling the increase in white blood cells): 2 weeks
   - Non-cytotoxic drugs: at least 5 × the half-life of the drug
8) Laboratory test results obtained within 14 days before registration meet all of the following requirements:

Laboratory Parameter	Requirement
AST	≤ 2.5 times the upper limit of the institutional reference range
ALT	≤ 2.5 times the upper limit of the institutional reference range
Total bilirubin	≤ 1.5 times the upper limit of the institutional reference range
Serum creatinine	≤ 1.5 times the upper limit of the institutional reference range (or estimated glomerular filtration rate [eGFR]* ≥ 25 mL/min/1.73 m^2)
Serum K	Within the institutional reference range**
Serum Mg	Within the institutional reference range**
Serum Ca (corrected for albumin)	Within the institutional reference range**

* eGFR (mL/min/1.73 m^2) 194 × serum creatinine $^{1.094}$ × age $^{0.287}$ (× 0.739 for females)

** Patients with electrolytes outside the institutional reference range will be eligible if these values are corrected upon retesting following any necessary supplementation.

9) Patients who can receive quizartinib orally.

<Exclusion criteria>

1) Diagnosis of acute promyelocytic leukemia.
2) Patients who developed AML in association with prior chemotherapy or radiotherapy given to treat another malignant tumor than AML (patients with treatment-related

AML). However, this shall not apply to patients with a history of MDS.

3) History of malignant tumor within 5 years before registration.
   * However, participation of the following patients in the study is allowed.
   - Curatively treated skin cancer other than malignant melanoma, carcinoma in situ, or cervical carcinoma in situ (The time to onset of AML is not considered when the standard therapy has been completed.)
   - Prostate cancer without local recurrence or progression (any of the cases in which hormonal therapy has been initiated, the tumor has been surgically removed, or the lesion has disappeared with radiotherapy)
4) Persistent, symptomatic Grade 2 or more severe non-hematological toxicity (excluding alopecia) from prior therapy.
5) Patients with graft-versus-host disease (GVHD) that is clinically significant or requiring treatment, those who need to start treatment for GVHD, those requiring intensified treatment for GVHD within 21 days before registration, or those with Grade 2 or more severe clinically significant or irreversible non-hematological toxicity related to HSCT.
6) History of or current symptomatic central nervous system involvement with clinical symptoms.
7) Disseminated intravascular coagulation, or other clinically significant coagulation abnormalities.
8) Prior treatment with quizartinib or prior participation in any clinical study of quizartinib.
9) Prior treatment with other FLT3 inhibitors (sorafenib or other FLT3 inhibitors under development) (This does not include midostaurin.)
10) Extensive surgery within 28 days before registration.
11) Radiation therapy within 28 days before registration.
12) History of or current cardiovascular disease as specified

below:

- QT corrected for heart rate using Fridericia's method (QTcF) interval of 450 ms or longer, determined as the average of three central electrocardiogram (ECG) measurements taken within 14 days before registration
- Heart rate of 50 beats/min or lower, determined as the average of three central ECG measurements taken within 14 days before registration (excluding patients with a cardiac pacemaker)
- Previous, current, or suspected long QT syndrome, or a family history of congenital long QT syndrome
- History of life-threatening ventricular arrhythmia, such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes
- Second or third degree heart block (This shall not apply to patients who have second or third degree heart block, but who have a cardiac pacemaker and have never experienced syncope or arrhythmia before.)
- History of myocardial infarction within 6 months before registration
- History of uncontrolled angina pectoris within 6 months before registration
- Class III or more severe congestive heart failure according to "Appendix 3 New York Heart Association (NYHA) Functional Classification"
- Left ventricular ejection fraction (LVEF) below 45% or the lower limit of the institutional reference range
- Uncontrolled hypertension
- Complete left or right bundle branch block

13) Active infection that is not well controlled with antibacterial, antifungal, or antiviral therapy.
14) Active liver disease (hepatitis B, hepatitis C, etc.)
15) Tested positive for human immunodeficiency virus (HIV) antibody within 120 days before registration.
16) Women of childbearing potential, or their male partners

	who are unable or unwilling to practice appropriate contraception using effective contraceptive methods (eg, barrier contraceptives combined with spermicides, intrauterine device) for the entire study period and 3 months after the last dose of the study drug. Women of non-childbearing potential (postmenopausal women with no menses for at least 2 years and women who have undergone hysterectomy etc. at least 1 month before registration) may be registered in the study. Male patients may not donate their sperm during the period from 14 days before registration to 105 days after the last dose of the study drug. Female patients may not donate their eggs during the period from 14 days before registration to 12 weeks after the last dose of the study drug. 17) Women found to be pregnant by a pregnancy test performed within 14 days before registration. 18) Women who may need to breastfeed during the study period and for 25 days after the last dose of the study drug. 19) Patients who are otherwise considered ineligible for the study in the opinion of the investigators (investigator or subinvestigator).
Dosage form, dose and route of administration:	<Dosage form> White film-coated tablets, each of which contains 20 mg AC220, or yellow film-coated tablets, each of which contains 30 mg AC220. <Regimen> Quizartinib will be administered at an initial dose of 30 mg/day. For patients receiving strong cytochrome P450 (CYP) 3A4 inhibitors, an initial dose of 20 mg/day will be used. Quizartinib will be orally administered once daily every morning. Treatment with quizartinib will be administered in

28-day cycles and continued until the withdrawal criteria are met.
If a patient vomits after taking a dose of the study drug, a replacement dose may not be given on the same day.
A patient who did not take the study drug at the usual hour of dosing (eg, forgot to take the dose) will be allowed to take the missed dose within 10 hours after the usual hour of dosing (for example, if the patient usually takes the drug at 7:00 or 8:00, he/she may take it by 17:00 or 18:00). In this case, the next dose of the study drug on the following day should be taken at least 12 hours after the time when the last dose was taken. If the patient does not take the missed dose by 10 hours after the usual hour of dosing, he/she should not take the study drug on that day and resume taking the drug on the following day. The patient may not take two doses at once on the day when the drug is resumed.

<Criteria for dose increase of the study drug>
The dose of quizartinib will be increased in accordance with the following criteria. A 12-lead ECG will be measured at least once weekly for the first 2 weeks after a dose increase to confirm the presence or absence of QTcF prolongation after the dose increase. When doing this, triplicate ECG recordings will be obtained.

Assessment criteria for dose increase on Day 16 of Cycle 1
Patients not concomitantly using strong CYP3A4 inhibitors:
The dose of quizartinib will be increased to 60 mg/day if all QTcF data (determined as the average of three measurements) taken by Day 15 of Cycle 1 are 450 ms or shorter.

Patients concomitantly using strong CYP3A4 inhibitors:
The dose of quizartinib will be increased to 30 mg/day if all QTcF data (determined as the average of three measurements) taken by Day 15 of Cycle 1 are 450 ms or shorter.

	<u>Assessment criteria for dose increase on Day 1 of Cycle 2</u> For patients who have not achieved CR, CRp, or CRi after at least 1 cycle of treatment with quizartinib and whose condition before the decision on dose increase satisfies the following requirements, the dose of quizartinib will be increased. • Absence of Grade 3 or more severe treatment-related non-hematological toxicity • 60 ms or shorter increase in QTcF interval from baseline • Absence of hypoplastic bone marrow upon the decision of a dose increase For patients who have relapsed after achieving CR, CRp, CRi, or partial remission (PR), and satisfy the above criteria, the dose of quizartinib may be increased. The dose will be increased to 60 mg/day if strong CYP3A4 inhibitors are not concomitantly used, and to 30 mg/day if strong CYP3A4 inhibitors are concomitantly used.
Study endpoints:	Primary endpoint: CRc rate (composite complete remission rate) Secondary endpoints: • Best response • Response rate • Overall survival • Event-free survival • Leukemia-free survival • Safety (Adverse events [AEs], laboratory data, vital signs, body weight, ECOG PS, 12-lead ECG) • Pharmacokinetics (plasma concentrations of quizartinib and its active metabolite, and pharmacokinetic parameters) • Biomarkers (plasma inhibitory activity of quizartinib on phosphorylated FLT3 and c-Kit proteins)
Planned sample size:	25 patients for Stage 1, and 16 patients for Stage 2; 41 patients in total

Statistical analyses:	Efficacy evaluation: In the efficacy analysis set, frequency tables will be prepared for the best response, CRc rate, and response rate (RR: defined as the proportion of patients whose best response is CR, CRp, CRi, or PR), and the confidence intervals (CIs) will be calculated. Safety evaluation: Safety will be evaluated in the safety analysis set. Concerning AEs that newly appear after the first dose of the study drug or that worsen relative to the pre-treatment state, frequency tables will be prepared by event (system organ class/preferred term), causality with the study drug, and grade according to the Common Terminology Criteria for Adverse Events (CTCAE). Concerning laboratory data, vital sign measurements, body weight, ECOG PS, and 12-lead ECG findings, frequency tables or shift tables will be prepared for categorical data, and summary statistics will be calculated for quantitative data. To evaluate QT prolongation, summary statistics of QTcF will be calculated, and frequency tables will be prepared according to the predefined categories. Pharmacokinetics: In the pharmacokinetic analysis set, summary statistics of the plasma concentrations of quizartinib and AC886 will be calculated by dose at each time point, and plasma concentration-time profiles will be prepared. Summary statistics of pharmacokinetic parameters will be calculated by dose at each time point. Biomarkers: In the biomarker analysis set, the measured values of the plasma inhibitory activity of quizartinib on phosphorylated FLT3 and c-Kit proteins will be summarized at each time point.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Full Expression
ALP	alkaline phosphatase
ALT	L alanine aminotransferase
AML	acute myeloid leukemia
AST	L aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
CR	complete remission
CRc	composite CR
CRi	CR with incomplete hematological recovery
CRO	Contract Research Organization
CRp	CR with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose limiting toxicity
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electric case report form
EDC	electronic data capturing
eGFR	estimated glomerular filtration rate
FLT3	FMS like tyrosine kinase 3
GCP	Good Clinical Practice
γ GT	γ glutamyl transferase
GVHD	graft versus host disease
hERG	human ether à go go related gene
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IKr	potassium current carried by channel formed from hERG subunits
IKs	potassium current carried by channel formed from KVLQT1 (KCNQ1) subunits and minK (KCNE1) b subunits
IRB	institutional review board
ITD	internal tandem duplication
LVEF	left ventricular ejection fraction
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NR	no response
OS	overall survival
PIA	plasma inhibitory activity
PK	pharmacokinetics
PR	partial remission

Abbreviation	Full Expression
PS	performance status
QT	interval between the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcF	QT corrected for heart rate using Fridericia's method
RET	ret proto oncogene
RTK	receptor tyrosine kinase
SAP	statistical analysis plan
SAVER	Serious Adverse Event Report
STAT5	signal transducer and activator of transcription 5
TdP	torsades de pointes
TEAE	treatment emergent adverse event
ULN	upper limit of normal
WT	wild type

List of Pharmacokinetic Parameters

Abbreviation	Full Expression
AUC	area under the plasma concentration time curve
AUCinf	area under the plasma concentration time curve up to infinity
AUCtau	area under the plasma concentration time curve during dosing interval
AUCtau, ss	area under the plasma concentration time curve during dosing interval at steady state
Cmax	maximum plasma concentration
Cmax, ss	maximum plasma concentration at steady state
Ctrough	trough plasma concentration
Tmax	time to reach maximum plasma concentration
Tmax, ss	time to reach maximum plasma concentration at steady state

List of Terms

Term	Definition
AC220	Development code of quizartinib
AC886	Active metabolite of quizartinib

1. INTRODUCTION

1.1 Background of This Study

Acute myeloid leukemia (AML) is a hematological malignant tumor characterized by autonomous growth of myeloid blast cells (myeloblasts) that are unable to differentiate or further develop into mature white blood cells, and its clinical presentation is diverse.[1)] According to "Cancer Registration and Statistics" of the Cancer Information Service, National Cancer Center, the crude prevalence rate of leukemia is 9.6 (11.4 for males and 7.9 for females) per 100 000 people in 2011 and it is increasing each year.[2)] The prevalence rate of AML by itself is unknown; however, acute leukemia accounts for about 80% of all leukemias, and AML accounts for approximately 80% of adult acute leukemia cases and 20% of pediatric acute leukemia cases. While AML has become a disease that is considered curable in recent years, the long-term survival rate after complete remission (CR) with chemotherapy in AML patients remains low at about 40%.[3)] This is attributable to frequent relapse after remission. How to prevent relapse is a major problem of chemotherapy. To solve this problem, many research studies have identified poor prognostic factors in attempts to stratify AML. In patients with poor prognostic factors, intensified treatment does not necessarily improve the prognosis. Therefore, it is necessary to develop molecular targeting drugs in line with the molecular platform that plays a key role in AML.[4),5),6)]

FMS-like tyrosine kinase 3 (FLT3) mutations, which are found in approximately 30% of AML patients, represent an important poor prognostic factor and are listed as gene abnormalities that can be searched in the World Health Organization (WHO) classification version 4.[5),6)] FLT3 is a Class III receptor tyrosine kinase (RTK), like v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), colony stimulating factor 1 receptor (CSF1R), and platelet-derived growth factor receptor (PDGFR), and contains an intracellular tyrosine kinase domain split in two by the juxtamembrane domain. FLT3 is primarily expressed on hematopoietic progenitor cells and is dimerized and activated by ligand binding, and then involved in hematocyte differentiation and proliferation as well as self-replication of hematopoietic stem cells.[7)] FLT3 molecules are expressed on the leukemia cell surface in most cases of AML and acute lymphocytic leukemia, and play a role in the survival and proliferation of leukemia cells. There are two main types of FLT3 mutations: FLT3-internal tandem duplication (FLT3-ITD), which involves repetition of part of the juxtamembrane domain, and kinase domain mutation (KDM), which involves point mutation or deletion of the aspartic acid residue at position 835 (D835) in the tyrosine kinase domain or surrounding residues.[7)]

These gene mutations cause FLT3 ligand-independent, constant activation of FLT3 molecules and contribute to the promotion of leukemia cell proliferation via activation of downstream signaling pathways, including signal transducer and activator of transcription 5 (STAT5), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT). Therefore, mutated FLT3 molecules are recognized as promising target molecules for the treatment of AML.[6)]

1.2 Study Rationale

1.2.1 Summary of the Investigational Drug

Quizartinib (development code: AC220), synthesized by Ambit Biosciences Corporation, is a Class III RTK inhibitor that has potent and selective FLT3 inhibitory activity. Quizartinib for the treatment of AML is currently under clinical development overseas and in Japan. Shown below is a brief summary of data from the major nonclinical and clinical studies that have been conducted overseas and in Japan.

1.2.1.1 Nonclinical Study Data

1.2.1.1.1 Pharmacology

In a biochemical binding assay using a panel of 441 kinases, quizartinib and its metabolite, AC886, exhibited the highest binding affinity for FLT3. The binding affinity of quizartinib for other Class III RTKs (eg, KIT, CSF1R/FMS, PDGFRβ, RET) was within 10-fold lower than that for FLT3, and quizartinib had little or no affinity for other kinases, or for other enzymes, receptors, or channels than kinases.
In human MV4-11 leukemia cell line with FLT3-ITD mutations treated with quizartinib and AC886, these compounds inhibited FLT3-ITD autophosphorylation, as well as FLT3-dependent cell proliferation. Following 28-day (once daily) repeated oral dosing of quizartinib in mice with flank solid tumors established by subcutaneously implanted MV4-11 cells, quizartinib inhibited tumor growth at 1 mg/kg and induced tumor regression at 3 mg/kg and 10 mg/kg. At 10 mg/kg, tumors did not regrow throughout the entire 32-day follow-up period after quizartinib dosing. Quizartinib administered in combination with chemotherapy (cytarabine and daunorubicin) was also confirmed to have superior antitumor activity and be well tolerated in the above-mentioned mouse model.

1.2.1.1.2 Safety Pharmacology Studies

In a telemetry study in cynomolgus monkeys, quizartinib dose-dependently prolonged the corrected QT interval (QTc) and transiently increased systemic blood pressure at 10 mg/kg or more; however, no hemodynamic or electrocardiographic (ECG) changes were seen at 3 mg/kg. In the assessment of potential effects of quizartinib and AC886 on potassium current carried by the channel formed from human ether-à-go-go related gene (hERG) subunits (IKr) channel-coded by hERG using a patch clamp approach in HEK293 cells overexpressing hERG, quizartinib did not inhibit the IKr channel, whereas AC886 inhibited the IKr channel concentration-independently (maximum inhibition: 30% to 40%). In the assessment of potential effects of quizartinib and AC886 on sodium current (INa), potassium current carried by the channel formed from KVLQT1 (KCNQ1) subunits and minK (KCNE1) b-subunits (IKs), and long-lasting calcium current (ICa-L), quizartinib inhibited IKs, and AC886 inhibited INa, IKs, and ICa-L. In ex vivo studies using rabbit heart preparations, quizartinib and AC886 caused increases in QTc interval at concentrations of more than 3 μM. It was thus suggested that the effects of the two compounds on potassium currents (IKs + IKr) would play a role in QTc prolongation.

1.2.1.1.3 Pharmacokinetics and Drug Metabolism

Plasma exposure of quizartinib was approximately dose proportional in mice, rats, dogs, and monkeys. In all examined species, quizartinib was converted to the active metabolite, AC886. Bioavailability of quizartinib across species ranged from 16% in monkeys to 40% in dogs. The low bioavailability of quizartinib in monkeys was considered to be related to the high metabolic clearance of quizartinib to the active metabolite AC886. The presence of food was suggested to enhance the fraction of administered quizartinib dose absorbed in rats. In rats given repeated doses, there was evidence of accumulated quizartinib, but no evidence of self-induced metabolism. Quizartinib and AC886 were shown to be highly bound to plasma proteins (> 99% in all species tested), and quizartinib was shown to poorly penetrate the brain in rats. Quizartinib was confirmed to be neither an inhibitor (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) nor an inducer (3A4 and 1A) of major human cytochrome P450 (CYP) isoenzymes. AC886 showed weak inhibitory activity against CYP2C8, but had no inhibitory activity against the other isoenzymes, which suggests that AC886 is unlikely to show inhibitory activity against CYPs at physiologic concentrations. Quizartinib and AC886 are substrates for CYP3A4, and quizartinib is metabolized by CYP3A4 to AC886.

On the other hand, CYP2B6, 2C8, 2C9, 2C19, 2D6, and 1A2 are found to be barely involved in the metabolism of quizartinib.

1.2.1.1.4 Toxicology

Quizartinib was tested in single-dose toxicity studies (rats, dogs, and monkeys) and repeated-dose toxicity studies (28-day and 90-day studies in rats, dogs, and monkeys), genetic toxicity studies (in vitro and in vivo), reproductive and developmental toxicity studies (rats), and in vitro neutral red uptake phototoxicity assay using a murine fibroblast line (3T3).

In repeated-dose toxicity studies, the principal organs affected were the lymphoid and hematopoietic organs in all species tested. In addition, toxicologic effects were observed in the kidneys, liver, and genital organs (ovary, vagina, and testis).

Target-organ toxicity appeared to be quizartinib dose- and time-dependent, and most toxicologic findings were reversible following a 28- or 30-day recovery period; however, slight decreases in red blood cell and white blood cell parameters, minimal bone marrow hypocellularity, and liver crystal deposition (only in dogs) persisted after the end of the recovery period. In 90-day studies, toxicologic findings were evident in high-dose rats and dogs at 10 mg/kg and 15 mg/kg, respectively, and included decreases in hematology parameters, increased liver enzymes, and histopathological changes in bone marrow and lymphoid organs. In 90-day studies in monkeys, the mortality and toxic signs were reported at 10 mg/kg/day, resulting in a dose reduction to 6 mg/kg/day during the dosing period; these toxicologic findings observed in monkeys were consistent with those seen in rats and/or dogs. The no adverse effect level (NOAEL) from 90-day repeated oral doses was established at 3 mg/kg/day in rats and monkeys and 5 mg/kg/day in dogs. The Cmax and AUC of quizartinib at the NOAEL were 0.82 μg/mL and 12.1 μg·h/mL in rats, 0.11 μg/mL and 0.727 μg·h/mL in monkeys, and 0.42 μg/mL and 3.93 μg·h/mL in dogs, respectively.

Quizartinib was evaluated for genotoxic potential; quizartinib was positive in bacterial reverse mutation assay, but was not genotoxic in chromosomal aberration assay in human lymphocytes, mammalian cell mutagenicity assay, or micronucleus assay in rats. In the mammalian cell mutagenicity assay, it was evaluated whether the positive result obtained from the bacterial reverse mutation assay could be reproduced or not. In mouse lymphoma L5178Y $TK^{+/}$ cells incubated with quizartinib, no substantial increases in mutation frequency were observed at doses up to the cytotoxicity limit, and quizartinib did not induce genetic mutations. Consequently, quizartinib is considered to have a low

genotoxic risk.
In embryo-fetal toxicity studies in rats, systemic edema was found in fetuses at the maximum dose of 6 mg/kg/day, in addition to decreased fetal weight and delayed skeletal ossification. The NOAEL for embryo-fetal development was considered to be 2 mg/kg/day.
In the neutral red uptake phototoxicity assay, quizartinib had a photo irritation factor of 3.13 and a mean photo effect of 0.122. These results suggested that the compound would have a "phototoxic potential" according to the guidelines at the time of the assay.[8),9),10)] However, a review of the assay data in accordance with the guidance on photosafety evaluation of pharmaceuticals issued on 21 May 2014[11)] resulted in the conclusion that quizartinib is not phototoxic.

1.2.1.2 Clinical Study Data

1.2.1.2.1 Overseas Phase 1 Study (Study CP0001)

Quizartinib was tested in 76 AML patients with treatment cycles of intermittent dosing (14 days on the drug followed by 14 days of rest) at doses of 12 mg/day to 450 mg/day, and 28-day continuous dosing at 200 and 300 mg/day.
Dose-limiting toxicities (DLTs) were pyrexia in 1 of 5 patients on intermittent dosing at 135 mg/day, Grade 3 QTc prolongation in 1 of 17 patients on continuous dosing at 200 mg/day, and Grade 3 QTc prolongation in 3 of 8 patients on continuous dosing at 300 mg/day. The maximum tolerated dose (MTD) was determined to be 200 mg/day continuous dosing.
The overall response rate (CR + partial remission [PR]) was 53% in FLT3-ITD positive patients and 14% in FLT3-ITD negative patients.
In this study, plasma specimens were collected from quizartinib-treated patients and were tested in an ex vivo assay of plasma inhibitory activity of quizartinib on FLT3 phosphorylation. Plasma from the patients suppressed FLT3-ITD and wild-type FLT3 (FLT3-WT) autophosphorylation activity. In cells expressing FLT3-WT, higher doses and longer exposures of quizartinib were necessary to eliminate detectable phosphorylated FLT3 as compared with FLT3-ITD-expressing cells.
Moreover, a subset of 20 AML patients in the study were evaluated for the effect of quizartinib on phosphorylated STAT5 (pSTAT5), using a whole blood-based assay. Quizartinib treatment decreased pSTAT5 levels in 10 of 11 FLT3-ITD positive patients and 7 of 9 FLT3-ITD negative patients. There was an enhanced effect on pSTAT5 inhibition in FLT3-ITD positive patients. These data suggest that quizartinib inhibits

pSTAT5 production regardless of FLT3-ITD mutation status in AML patients.

1.2.1.2.2 Overseas Phase 2 Studies (Studies AC220-002 and 2689-CL-2004)

In Study AC220-002 conducted in 333 patients with relapsed or refractory AML, 12 patients received 28-day continuous dosing at 200 mg/day, which is the MTD determined in Study CP0001, and Grade 3 QTc prolongation was reported at this dose in 42% of patients in Study AC220-002. The study demonstrated that the incidence of QTc prolongation tended to be higher in females than in males. To address this issue, the dose of quizartinib was reduced to 135 mg/day for males and 90 mg/day for females during the course of Study AC220-002. After dose reduction, 1 female patient on continuous dosing at 90 mg/day, concomitantly with a strong CYP3A4 inhibitor, experienced Grade 4 QTc prolongation (torsades de pointes [TdP]).

In Study AC220-002, patients were divided into 2 cohorts according to age and previous treatment status. Specifically, AML patients aged 60 years or older with relapsed or refractory AML after one first-line chemotherapy regimen, were enrolled in Cohort 1, while AML patients aged 18 years or older with relapsed or refractory AML after salvage regimen, or relapsed AML after hematopoietic stem cell transplant (HSCT) were enrolled in Cohort 2. In Cohort 1, the composite CR (CRc) rate was 57% in a subset of FLT3-ITD positive patients, with a median overall survival of 25.3 weeks. In Cohort 2, the CRc rate was 46% in a subset of FLT3-ITD positive patients, with a median overall survival of 24.0 weeks. In Cohort 2, 35% of FLT3-ITD positive patients proceeded to HSCT, and almost all (94%) of those proceeding to HSCT achieved CRc or PR with quizartinib treatment, with a 1-year survival rate of 39%.

Study 2689-CL-2004 was conducted in 76 FLT3-ITD positive patients with relapsed or refractory AML, who were assigned to 28-day cycles of 30 or 60 mg/day continuous dosing of quizartinib (for both males and females) to evaluate the efficacy and safety of quizartinib at lower doses than those tested in Study AC220-002. In the study, the incidence of QTc prolongation was much lower than that observed in Study AC220-002, indicating that the risk of QTc prolongation was dose-dependent (Table 1.2-1). The study also demonstrated that the CRc rates were comparable to those observed in Study AC220-002 (Table 1.2-2). In Study 2689-CL-2004 as well, 34% of patients proceeded to HSCT, and the patients who underwent HSCT tended to have a longer survival than those who did not.

Common adverse events (AEs) reported in Studies AC220-002 and 2689-CL-2004 were nausea, diarrhea, vomiting, pyrexia, fatigue, edema peripheral, febrile neutropenia,

anemia, and electrocardiogram QT prolonged. Although the hematologic toxicities appear to be associated with the underlying disease, AML, data suggest delayed recovery or continued suppression of absolute neutrophil count (ANC) and platelets as a consequence of continued treatment with quizartinib.

Table 1.2-1 Maximum Values of QT Corrected for Heart Rate Using Fridericia's Method (QTcF) and Maximum Changes from Baseline in QTcF in Two Phase 2 Studies

Daily dose of quizartinib	Study AC220 002 (Cohort 2)			Study 2689 CL 2004	
	90 mg/day (N 57) † Female	135 mg/day (N 67) † Male	200 mg/day (N 12)	30 mg/day (N 38)	60 mg/day (N 36)*
Maximum QTcF (ms)					
> 480, ≤ 500 (Grade 2)	21%	13%	33%	5%	14%
> 500 (Grade 3) † Asymptomatic	21%	15%	42%	5%	3%
Maximum change in QTcF from baseline (ms)					
≤ 30	9%	9%	0%	47%	39%
> 30, ≤ 60	46%	51%	8%	47%	42%
> 60	46%	39%	92%	5%	19%

* Two patients in the 60 mg/day group were randomized but never treated with quizartinib.

Table 1.2-2 Composite Complete Remission and Partial Response Rates in Two Phase 2 Studies

Daily dose of quizartinib	Study AC220 002 (Cohort 2)			Study 2689 CL 2004	
	90 mg/day (N 57) † Female	135 mg/day (N 67) † Male	200 mg/day (N 12)	30 mg/day (N 38)	60 mg/day (N 38)
CRc rate	47%	45%	42%	47%	47%
PR rate	25%	28%	50%	13%	24%

1.2.1.2.3 Overseas Phase 3 Study (Study AC220-007: QuANTUM-R)

Study AC220-007 is a multicenter, randomized, open-label, two-arm, Phase 3 study to compare the effect of quizartinib monotherapy versus salvage chemotherapy on overall survival in patients with FLT3-ITD positive AML that is refractory or has relapsed within 6 months after first-line therapy with or without consolidating HSCT. Treatment with quizartinib is started at a dose of 30 mg/day and the dose may be increased to 60 mg/day based on the safety and efficacy requirements. If a strong CYP3A4 inhibitor is concomitantly used, treatment with quizartinib is started at a dose of 20 mg/day and the dose may be increased to 30 mg/day. This study is ongoing and the updated status as of 22 Jan 2016 is shown below.

Of 326 target subjects, 160 subjects were enrolled in the study; male subjects accounted for 46% and most subjects were white (134 of 160 subjects, 84%) and aged 18 to 60

years (96 of 160 subjects, 60%, median: 55 years). The majority of the subjects did not have prior HSCT (125 of 160 subjects, 78%). A total of 99 subjects (62%) discontinued the study treatment. Major reasons for discontinuation of treatment were a lack of response/disease progression (39 of 99 subjects, 39%) and relapse (22 of 99 subjects, 22%). There were 19 deaths due to AEs. The AEs resulting in death included infections and infestations in 10 subjects, blood and lymphatic system disorders, cardiac arrest/failure, graft-versus-host disease (GVHD) in gastrointestinal tract, and respiratory distress/failure in 2 subjects each, and acute kidney injury in 1 subject. Of these AEs, GVHD in gastrointestinal tract, infections and infestations (bronchopulmonary aspergillosis and necrotising fasciitis), cardiac failure acute, and blood and lymphatic system disorders (thrombocytopenia) were assessed to be related to quizartinib. A total of 161 SAEs were reported, and the most common SAE was febrile neutropenia (29 of 160 subjects, 18%). The profile of reported AEs is consistent with safety data from clinical studies that have previously been conducted, and no new safety concerns have been identified. The Safety Data Monitoring Committee assessed this study as, “there are no concerns about the continued conduct of the study” at the meeting held in Jun 2016, and a total of 255 subjects were randomized as of 06 Sep 2016.

1.2.1.2.4 Japanese Phase 1 Studies (Studies AC220-A-J101 and AC220-A-J102)

Study AC220-A-J101 is a multicenter, open-label, Phase 1 study to evaluate the safety and pharmacokinetics of quizartinib monotherapy that assesses the recommended dose for subsequent phase clinical studies in Japanese AML patients. Since this was the first clinical study in Japanese AML patients, treatment with quizartinib was started at a dose of 20 mg/day, which was lower than the dose used in Study AC220-007, taking safety into consideration. Based on the results of DLT assessment etc. at each dose cohort, the dose was increased up to 60 mg/day. The dose of 60 mg/day was the maximum dose used in Studies 2689-CL-2004 and AC220-007.

There were no reports of protocol-specified DLTs, including Grade 3 or more severe QTcF prolongation, based on the results of DLT assessment in each cohort of 20 mg/day, 30 mg/day, and 60 mg/day (3 subjects, 3 subjects, and 3 subjects, respectively) (end date of DLT assessment in the 60 mg/day cohort: 17 Nov 2016).

Study AC220-A-J102 is a multicenter, open-label, Phase 1 study to evaluate the safety and pharmacokinetics of quizartinib in combination with standard remission induction and consolidation therapy that assesses the dose for subsequent phase clinical studies in Japanese patients with newly diagnosed AML. Chemotherapy in this study consisted of

remission induction therapy and consolidation therapy given for up to 2 and 4 cycles, respectively, each of which was 28 days long. Since this was the first clinical study of quizartinib in Japanese patients with newly diagnosed AML, treatment with quizartinib was started at a dose of 20 mg, which had been the initial dose used in Study AC220-A-J101, and was administered in combination with standard therapy, taking the subjects' safety into consideration.

1.2.1.2.5 Pharmacokinetics

Pharmacokinetic data of quizartinib and its active metabolite AC886 from clinical studies in AML patients and healthy volunteers have been evaluated. After administration of quizartinib, the plasma concentrations of quizartinib and AC886 increased rapidly (Tmax of quizartinib, 2 to 8 hours post quizartinib dosing during the first day of dosing). Quizartinib and AC886 had terminal elimination half-lives of approximately 3 days, resulting in approximately 4-fold accumulation from the first day of dosing for exposure at the steady state after daily dosing. Plasma exposure to both quizartinib and AC886 was generally proportional with the dose in the tested dose range of 30 mg to 90 mg. Overall, Cmax and AUC showed moderate to high variability. Plasma concentrations of AC886 at the steady state paralleled quizartinib levels with a plasma concentration ratio of AC886 to quizartinib (AC886/quizartinib) of 0.5. AC886 is the only major metabolite of quizartinib in the circulation. Quizartinib was mainly eliminated by non-renal clearance. The presence of concomitant ketoconazole, a strong CYP3A4 inhibitor, increased the observed AUCinf of quizartinib approximately 2-fold. The presence of concomitant fluconazole, a moderate CYP3A4 inhibitor, increased the observed AUCinf of quizartinib approximately 1.2-fold.

1.2.1.3 Known and Expected Risks and Benefits

AEs that were particularly frequently reported in previous clinical studies were body as a whole general disorders (eg, pyrexia and fatigue) and gastrointestinal disorders (eg, nausea, diarrhea, and vomiting). In addition, blood disorders (eg, anemia, neutropenia, and thrombocytopenia), neutrophilic dermatosis/pyoderma gangrenosum, effects of cytopenia (eg, increased risk of infection and hemorrhage), and QTc prolongation have also been reported.

Although the hematotoxicities may be associated with AML, safety reports of Study AC220-002 indicate delayed recovery of neutrophil and platelet counts as a consequence of continued treatment with quizartinib in many patients.

SAEs related to bone marrow depression (eg, neutropenia, bone marrow hypocellularity, lymphopenia, anemia, hemorrhage, thrombocytopenia, and pancytopenia), and/or infections (particularly, but not exclusively, fungal and other opportunistic infections, Gram negative bacterial infections, and bacteremia/sepsis) have been reported in quizartinib clinical studies. Reports of infections have often been in the context of neutropenia, pyrexia, or both. Investigators should recognize that AML may raise the risk of infection. Attention should also be paid to infections from diverse pathogens in different organ systems (including sepsis and bacteremia).
There are also reports of SAEs related to hemorrhage (eg, epistaxis, hemoptysis, melena, gastrointestinal hemorrhage, and intracranial hemorrhage).
QTc prolongation is as stated in "1.2.1.2.2 Overseas Phase 2 Studies (Studies AC220-002 and 2689-CL-2004)." Treatment with quizartinib may induce TdP depending on the concomitant administration of QTc prolonging drugs, a history of TdP, preexisting QTc prolongation, congenital long QT syndrome, or other clinical states of physiologic stress (eg, pneumonia and other infections), administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia.
The efficacy of quizartinib at various doses was assessed in three overseas clinical studies in patients with relapsed or refractory AML (Studies CP0001, AC220-002, and 2689-CL-2004). Based on combined data from FLT3-ITD positive and negative patients, the CRc rate was 13% to 63%. The median duration of remission was 10.4 to 13.3 weeks. The median overall survival (OS) was 8.6 to 24.6 weeks. Quizartinib was more effective in FLT3-ITD positive patients, with a CRc rate of 24% to 52%. Based on these findings, it was considered that quizartinib would provide clinically significant sustained effects in patients with relapsed or refractory AML.

1.2.2 Study Rationale

An international guideline for the treatment of AML (NCCN Clinical Practice Guideline in Oncology: Acute Myeloid Leukemia) has been established, and overseas and Japanese treatment strategies are generally the same. Patients with relapsed or refractory AML are treated with monotherapy or combination therapy with cytarabine, mitoxantrone, etoposide, fludarabine, aclarubicin, gemtuzumab ozogamicin, and others. None of these therapies, however, provide an adequate therapeutic effect. No standard treatment has been established for these patients.[12)] There are also no molecular targeting drugs that can be used for newly diagnosed AML patients, in whom a high relapse rate is still a problem.

As mentioned above, it has been confirmed that quizartinib is highly effective and safe at 30 mg and 60 mg doses in patients with FLT3-ITD positive relapsed or refractory AML in the overseas Study 2689-CL-2004, while Study AC220-007 is currently underway in patients with relapsed or refractory AML, mainly in the US and Europe.
In Japan, Study AC220-A-J101 in patients with relapsed or refractory AML and a Phase 1b clinical study of quizartinib in combination with standard therapy in Japanese patients with newly diagnosed AML (Study AC220-A-J102) are currently underway. As mentioned above, DLT assessment at all doses up to 60 mg/day has been completed in Study AC220-A-J101. The present study will be conducted primarily to confirm the efficacy of the regimen that was used in the quizartinib group in the preceding Study AC220-007, in Japanese patients. Treatment with the study drug in patients in the present study will start after DLT assessment in Study AC220-A-J101 has been completed and quizartinib has been confirmed to be safe at doses of up to 60 mg/day.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1 Study Objectives

2.1.1 Primary Objective

To evaluate the CRc rate (defined as the proportion of patients whose best response is CR, CR with incomplete platelet recovery [CRp], or CR with incomplete hematological recovery [CRi]) after treatment with quizartinib as multiple-dose monotherapy in Japanese patients with FLT3-ITD positive relapsed or refractory AML.

2.1.2 Secondary Objectives

- To evaluate the overall survival with quizartinib
- To evaluate the event-free survival with quizartinib
- To evaluate the leukemia-free survival with quizartinib
- To evaluate the safety of quizartinib
- To evaluate the pharmacokinetics of quizartinib
- To evaluate quizartinib-related biomarkers

2.2 Study Hypotheses

To confirm that the CRc rate with quizartinib monotherapy is at least 23.5% in Japanese patients with FLT3-ITD positive relapsed or refractory AML.

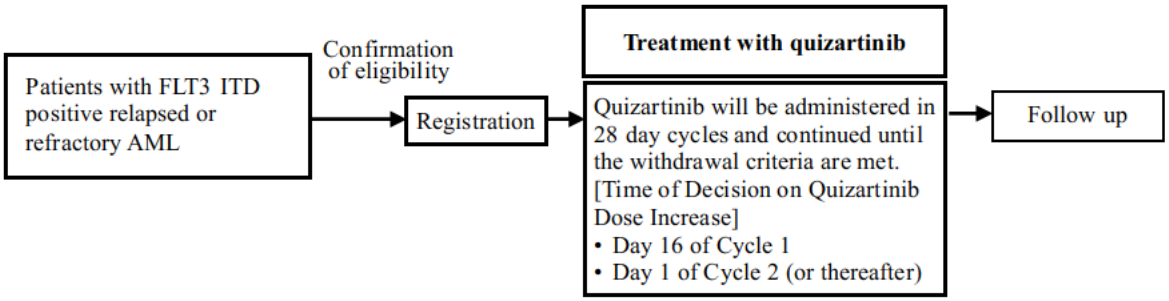
3. STUDY DESIGN

3.1 Overall Design

This is a multicenter, open-label, single-arm, Phase 2 clinical study to assess the efficacy and safety of quizartinib monotherapy in patients with FLT3-ITD positive AML who have relapsed or are found to be refractory within 6 months after initial remission induction therapy (it is not taken into consideration whether they have received HSCT or not).

Quizartinib will be administered at an initial dose of 30 mg/day. For patients receiving strong CYP3A4 inhibitors, an initial dose of 20 mg/day will be used. Quizartinib will be orally administered once daily every morning. Treatment with quizartinib will be administered in 28-day cycles and continued until "5.7.1 Discontinuation Criteria for Treatment with the Study Drug" are met.

Whether to increase or maintain the dose of quizartinib will be determined on Day 16 of Cycle 1 and Day 1 of Cycle 2 in accordance with "5.2.4.3 Criteria for Dose Increase of the Study Drug." A 12-lead ECG will be measured at least once weekly for the first 2 weeks after a dose increase to carefully confirm the presence or absence of QTcF prolongation after the dose increase. When doing this, triplicate ECG recordings will be obtained.



This study will be conducted using a two-stage design. In Stage 1, interim analysis will be performed when 25 patients have been included in the efficacy analysis set. As a result, the study will be terminated both if CR, CRp, or CRi (CRc) is achieved in 3 or fewer patients (the treatment will be determined to be ineffective), or if CR, CRp, or CRi (CRc) is achieved in 11 or more patients (the treatment will be determined to be effective). Meanwhile, if CRc is achieved in 4 to 10 patients, registration of patients will be continued until 41 patients are included in the efficacy analysis set (addition of 16 patients in Stage 2). When the study proceeds to Stage 2, the results of the final analysis

will be assessed as follows: Concerning the 41 patients included in the efficacy analysis set, if CRc is achieved in 15 or more patients, the treatment is determined to be effective (rejection of the null hypothesis). The details of interim analyses are shown in "11.4 Interim Analysis."

Registration of patients will be continued during the course of the interim analysis. If it is decided to terminate the study early, the registration of patients will be discontinued; however, treatment with the study drug in patients who continue receiving the study drug will be continued until "5.7.1 Discontinuation Criteria for Treatment with the Study Drug" are met.

3.2 Discussion of Study Design

3.2.1 Rationale for the Dose and Dosage of the Study Drug

In the overseas Phase 1 study (Study CP0001), quizartinib was administered intermittently at doses of 12 mg/day to 450 mg/day (14 days on treatment, followed by 14 days of rest) and at doses of 200 mg/day and 300 mg/day for 28 consecutive days in 76 AML patients, and the maximum tolerated dose of quizartinib was 200 mg/day that was administered for 28 consecutive days. In the overseas Phase 2 study (Study AC220-002), quizartinib was administered at a dose of 200 mg/day for 28 consecutive days in 333 AML patients, and Grade 3 QTc prolongation was reported in 42% of the patients. The incidence of QTc prolongation tended to be higher in female than male patients, and the dose of quizartinib was reduced to 135 mg/day in male patients and 90 mg/day in female patients during the course of Study AC220-002. TdP associated with Grade 4 QTc prolongation occurred in one female patient receiving consecutive-day treatment with quizartinib at a dose of 90 mg/day concomitantly with a strong CYP3A4 inhibitor. Therefore, in the overseas Phase 2b study (Study 2689-CL-2004), quizartinib was administered at 30 mg/day or 60 mg/day for 28 consecutive days to assess the safety and efficacy of quizartinib at lower doses. As a result, the incidence of QTc prolongation significantly decreased in the 30 mg and 60 mg groups compared with the higher dose groups (90 mg to 200 mg) established in Study AC220-002, which indicated that the potential risk of QTc prolongation was dose-dependent. The incidence of increased QTc interval to longer than 500 ms was 5% and 3% in the 30 mg and 60 mg groups, respectively, while the incidence of change in QTc interval of longer than 60 ms from baseline was 3% and 19%, respectively (Table 1.2-1). It was also clarified that the CRc rate in the 30 mg and 60 mg groups was equivalent to that in the high dose groups (90 mg to 200 mg) in Study AC220-002 (Table 1.2-2).

Increased QT/QTc interval to longer than 500 ms and an increase of longer than 60 ms in QT/QTc interval from baseline are important changes to decide whether to conduct a clinical study or not.[13)] According to the results of Study 2689-CL-2004, the incidence of increased QTc interval to longer than 500 ms was as low as 5% or less in the 30 mg and 60 mg groups, and the incidence of a longer than 60 ms increase in QTc interval from baseline was lower in the 30 mg and 60 mg groups than in the 90 mg or higher dose groups. Based on these data, it was considered that quizartinib is tolerated at doses of 30 mg and 60 mg, and the initial dose of 30 mg was chosen in this study. The rationale for setting 20 mg/day as the initial dose of quizartinib for patients concomitantly using strong CYP inhibitors is shown below.

In a drug-drug interaction study in healthy adult subjects, ketoconazole (strong CYP3A4 inhibitor) or fluconazole (moderate CYP3A4 inhibitor) was administered as multiple doses, followed by quizartinib as a single dose; concomitant treatment with ketoconazole or fluconazole resulted in 1.17-fold or 1.11-fold Cmax, respectively, and 1.94-fold or 1.20-fold AUCinf, respectively, compared with quizartinib monotherapy. Based on this result, it was estimated that the steady-state plasma quizartinib concentration following administration of multiple-dose quizartinib concomitantly with ketoconazole or fluconazole would increase by 1.86-fold or 1.21-fold, respectively, for Cmax and by 1.96-fold or 1.21-fold, respectively, for $AUC_{0\ 24}$, compared with quizartinib monotherapy. This result indicates that exposure to quizartinib nearly doubles when quizartinib is concomitantly used with strong CYP3A4 inhibitors, and it was therefore considered appropriate to administer quizartinib at a dose of 20 mg/day, which is about half the dose, in the presence of strong CYP inhibitors. Meanwhile, exposure to quizartinib concomitantly used with moderate CYP3A4 inhibitors is limited, and it was therefore considered unnecessary to reduce the dose of quizartinib in the presence of moderate CYP3A4 inhibitors. The initial dose of quizartinib in Study AC220-007 was set at 30 mg/day (20 mg/day in the presence of strong CYP3A4 inhibitors) for the same reason.

3.2.2 Rationale for the Method of Dose Increase of the Study Drug

In Study 2689-CL-2004, the CRc rate at the final analysis was 47% in both the 30 mg and 60 mg groups; however, CRc was not achieved in 63% (24/38 patients) of the patients in the 30 mg group after the end of Cycle 1, and the dose was increased to 60 mg accordingly. Meanwhile, the proportion of patients in the 60 mg group who did not achieve CRc after the end of Cycle 1 and for whom the dose was increased to 90 mg was 19% (7/36 patients). Although these data are limited, a higher tendency for efficacy

was observed in the 60 mg group than the 30 mg group when it was measured by other endpoints such as the transplantation rate, PR rate, duration of CRc, and median OS, and the 60-mg dose is thus likely to be superior to the 30-mg dose in terms of efficacy.
When the relationship between exposure to AC220 and its active metabolite AC886 and the efficacy on Day 15 of Cycle 1 was compared between the two dose groups, no significant correlation between the 30 mg and 60 mg groups was observed in the CRc rate after the end of Cycle 1, or $AUC_{0\ 24h}$ of AC220, $AUC_{0\ 24h}$ of AC886, or the sum of $AUC_{0\ 24h}$ of AC220 and AC886 on Day 15 of Cycle 1, which suggests that there is no difference in exposure between these dose groups at the end of Cycle 1. Accordingly, it is considered that there is no great difference in efficacy when quizartinib is administered at an initial dose of 30 mg and increased to 60 mg on Day 16 of Cycle 1 and when quizartinib is administered at an initial dose of 60 mg.
In addition, when the relationship between drug concentrations and QTc interval was evaluated using the data from Study 2689-CL-2004, a linear relationship between prolongation of QTc interval and plasma AC220 concentrations was found. The half-life of AC220 was approximately 3 days, and quizartinib exposure reached a steady state on Day 15 of Cycle 1 in both the 30 mg and 60 mg groups. Therefore, prolongation of QTc interval caused by AC220 was estimated to reach a peak on Day 15 of Cycle 1. Data from Study 2689-CL-2004 did not show any significant correlation between plasma AC886 concentrations and prolongation of QTc interval.
In view of these data, it was considered possible to increase the dose of quizartinib from 30 mg to 60 mg on Day 16 of Cycle 1 or later based on the assessment on Day 15 of Cycle 1, when the plasma quizartinib concentration reaches a steady state, in accordance with "5.2.4.3 Criteria for Dose Increase of the Study Drug."

3.2.3 Rationale for Sample Size

Refer to Section "11.5 Determination of Sample Size."

4. STUDY POPULATION

Prior to assessment of eligibility for enrollment in the study, patients must sign the informed consent form (ICF) provided by the study center, and date it.
patients who meet all of the following inclusion criteria and do not fit any of the exclusion criteria and who provide written informed consent of their free will are eligible for the study.

4.1 Inclusion Criteria

Patients must satisfy all of the following criteria to be included in the study:

1) Provision of written informed consent for participation in the study.
2) Patients aged 20 years or older when consent is obtained.
3) Primary AML patients or AML patients with a history of myelodysplastic syndrome (MDS).
4) AML patients who have first relapsed within 6 months after achieving remission with initial remission induction therapy or those who are refractory to all therapies given prior to the start of the study and failed to achieve remission. The initial remission induction therapy must be a regimen containing at least 1 cycle of standard-dose treatment with anthracyclines or mitoxantrone. It is not taken into consideration whether they have HSCT or not.
   - Definition of refractory to treatment
     - Patients who have less than 50% reduction in bone marrow blasts and have failed to achieve CR, CRp, or CRi after 1 cycle of treatment.
     - Patients who have failed to achieve CR, CRp, or CRi after 2 cycles of treatment.
   - Definition of first relapse (within 6 months after achieving remission)
     - Patients who have achieved CR, CRp, or CRi after initial remission induction therapy and have relapsed within 6 months. It is not taken into consideration whether they have received consolidation therapy, maintenance therapy, or HSCT or not.
     - The duration of remission is defined as the day of the bone marrow test when CR, CRp, or CRi was confirmed or the day of HSCT to the day of the bone marrow test when relapse was confirmed or the day of reappearance of leukemic blasts in the peripheral blood.
5) Patients with mutations of the FLT3-ITD gene in bone marrow or peripheral blood.
   * A specimen for the FLT3-ITD mutation test will be submitted to Navigate BioPharma Services, Inc. (Navigate BioPharma), the central laboratory, to test mutations in the FLT3-ITD gene. However, patients who have been confirmed to be FLT3-ITD positive in the FLT3-ITD testing previously performed at another testing company or the central laboratory, SRL Inc. (SRL), may be assessed for eligibility for the study without waiting for the result of measurement at Navigate BioPharma.
6) Eastern Cooperative Oncology Group performance status (ECOG PS) score 0 to 2

(refer to "Appendix 2").

7) Patients in whom the intervals listed below can be achieved between the last dose or application of prior therapy and the first dose of the study drug in the study:
   - Cytotoxic drugs (excluding hydroxycarbamide used for the purpose of controlling the increase in white blood cells): 2 weeks
   - Non-cytotoxic drugs: at least 5 × the half-life of the drug
8) Laboratory test results obtained within 14 days before registration meet all of the following requirements:

Laboratory Parameter	Requirement
AST	≤ 2.5 times the upper limit of the institutional reference range
ALT	≤ 2.5 times the upper limit of the institutional reference range
Total bilirubin	≤ 1.5 times the upper limit of the institutional reference range
Serum creatinine	≤ 1.5 times the upper limit of the institutional reference range (or estimated glomerular filtration rate [eGFR]* ≥ 25 mL/min/1.73 m^2)
Serum K	Within the institutional reference range**
Serum Mg	Within the institutional reference range**
Serum Ca (corrected for albumin)	Within the institutional reference range**

* eGFR (mL/min/1.73 m^2) 194 × serum creatinine $^{1.094}$ × age $^{0.287}$ (× 0.739 for females)
** Patients with electrolytes outside the institutional reference range will be eligible if these values are corrected upon retesting following any necessary supplementation.

9) Patients who can receive quizartinib orally.

Rationale

1), 9) To ensure the eligibility as a study patient and for ethical considerations.
2) Twenty is considered the minimum age for patients to be able to provide appropriate informed consent based on their own decision.
3) to 6) To appropriately evaluate the efficacy of quizartinib in Japanese patients with FLT3-ITD positive relapsed or refractory AML.
7) To ensure that patients are in a stable physiological condition at the time of registration based on the "Guidelines for the Clinical Evaluation of Anticancer Drugs.[14)]"
8) To ensure that organ functions allowing the appropriate evaluation of patient safety have been maintained based on the "Guidelines for the Clinical Evaluation of Anticancer Drugs.[14)]"

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be disqualified from entering the study:

1) Diagnosis of acute promyelocytic leukemia.
2) Patients who developed AML in association with prior chemotherapy or radiotherapy given to treat another malignant tumor than AML (patients with treatment-related AML). However, this shall not apply to patients with a history of MDS.
3) History of malignant tumor within 5 years before registration. However, participation of the following patients in the study is allowed.
   - Curatively treated skin cancer other than malignant melanoma, carcinoma in situ, or cervical carcinoma in situ (The time to onset of AML is not considered when the standard therapy has been completed.)
   - Prostate cancer without local recurrence or progression (any of the cases in which hormonal therapy has been initiated, the tumor has been surgically removed, or the lesion has disappeared with radiotherapy)
4) Persistent, symptomatic Grade 2 or more severe non-hematological toxicity (excluding alopecia) from prior therapy.
5) GVHD that is clinically significant or requiring treatment, those who need to start treatment for GVHD, those requiring intensified treatment for GVHD within 21 days before registration, or those with Grade 2 or more severe clinically significant or irreversible non-hematological toxicity related to HSCT.
6) History of or current symptomatic central nervous system involvement with clinical symptoms.
7) Disseminated intravascular coagulation, or other clinically significant coagulation abnormalities.
8) Prior treatment with quizartinib or prior participation in any clinical study of quizartinib.
9) Prior treatment with other FLT3 inhibitors (sorafenib or other FLT3 inhibitors under development) (This does not include midostaurin.)
10) Extensive surgery within 28 days before registration.
11) Radiation therapy within 28 days before registration.
12) History of or current cardiovascular disease as specified below:
    - QTcF interval of 450 ms or longer, determined as the average of three central ECG measurements taken within 14 days before registration
    - Heart rate of 50 beats/min or lower, determined as the average of three central

ECG measurements taken within 14 days before registration (excluding patients with a cardiac pacemaker)

- Previous, current, or suspected long QT syndrome, or a family history of congenital long QT syndrome
- History of life-threatening ventricular arrhythmia, such as ventricular tachycardia, ventricular fibrillation, or TdP
- Second or third degree heart block
  (This shall not apply to patients who have second or third degree heart block, but who have a cardiac pacemaker and have never experienced syncope or arrhythmia before.)
- History of myocardial infarction within 6 months before registration
- History of uncontrolled angina pectoris within 6 months before registration
- Class III or more severe congestive heart failure according to "Appendix 3 New York Heart Association (NYHA) Functional Classification"
- Left ventricular ejection fraction (LVEF) below 45% or the lower limit of the institutional reference range
- Uncontrolled hypertension
- Complete left or right bundle branch block

13) Active infection that is not well controlled with antibacterial, antifungal, or antiviral therapy.
14) Active liver disease (hepatitis B, hepatitis C, etc.)
15) Tested positive for human immunodeficiency virus (HIV) antibody within 120 days before registration.
16) Women of childbearing potential, or their male partners who are unable or unwilling to practice appropriate contraception using effective contraceptive methods (eg, barrier contraceptives combined with spermicides, intrauterine device) for the entire study period and 3 months after the last dose of the study drug.
    Women of non-childbearing potential (postmenopausal women with no menses for at least 2 years and women who have undergone hysterectomy etc. at least 1 month before registration) may be registered in the study.
    Male patients may not donate their sperm during the period from 14 days before registration to 105 days after the last dose of the study drug. Female patients may not donate their eggs during the period from 14 days before registration to 12 weeks after the last dose of the study drug.
17) Women found to be pregnant by a pregnancy test performed within 14 days before

registration.

18) Women who may need to breastfeed during the study period and for 25 days after the last dose of the study drug.
19) Patients who are otherwise considered ineligible for the study in the opinion of the investigators.

Rationale

1) to 18) Established to appropriately evaluate the efficacy of quizartinib, taking the safety of the use of quizartinib into consideration.
16) to 18) Established because effects of quizartinib on the fetus and nursing babies cannot be ruled out. Breastfeeding women, independent of whether they interrupt breastfeeding or not, are not eligible for participation in the study.
19) Established so that the investigators can determine the eligibility for participation in the study from a comprehensive standpoint with careful consideration for patient safety.

5. STUDY TREATMENT

5.1 Assigning Patients to Treatments and Blinding

5.1.1 Treatment Groups

This is a single-arm study.

5.1.2 Method of Treatment Allocation

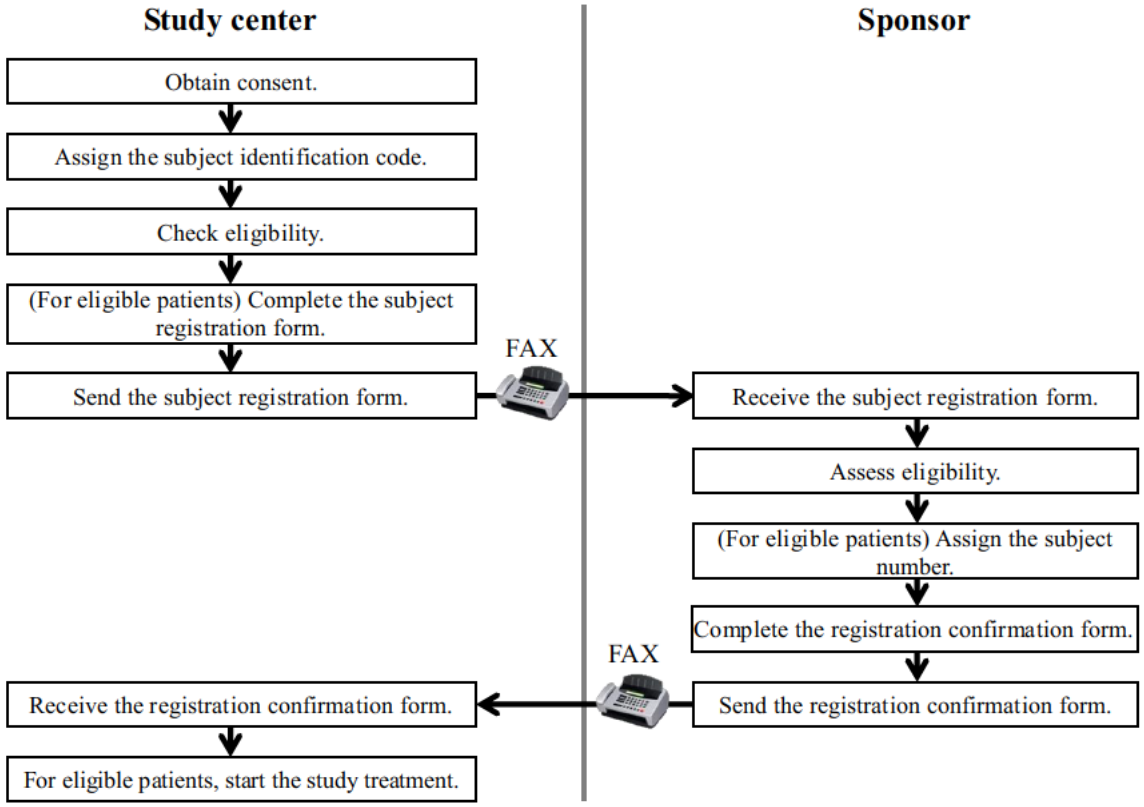
This is a single-arm study and randomization will therefore not be performed.
Registration of patients will be performed via fax. The procedure for patient registration is shown in Figure 5-1.
After obtaining written informed consent from each patient, the investigators will assign a subject identification code to the patient. If the above-stated patient is assessed to be eligible for the study, the investigators will enter the necessary information on the patient in the subject registration form and send it to the sponsor by fax.
The sponsor will check the eligibility of the patient in the light of the inclusion and exclusion criteria for the study based on the entries in the received subject registration form. If there are any questions about the entries in the registration form, the sponsor should immediately contact the investigators to make inquiries. When the sponsor determines that the patient is eligible for the study, the sponsor will register the patient and assign the subject number.

The sponsor will immediately fax the registration confirmation form together with the result of the eligibility assessment to the investigator; the confirmation form should include the date of registration, subject number, and dose of the study drug for patients assessed to be eligible, and the fact that the patient is not eligible and the reason for it for patients assessed to be ineligible. The investigators will explain the reason for ineligibility to patients assessed to be ineligible by the sponsor.

Address for sending the subject registration form
(the sponsor's address)
Working hours: Monday to Friday, 9:00 to 17:30
(closed on Saturdays, Sundays, and public holidays)
FAX: [redacted]
TEL: [redacted]

The investigators may not dispense the study drug to a patient until the patient is registered.
If any patient provides informed consent but is not registered, the investigators will describe the reason why the patient is not registered in the medical record. The patient will not be included in the number of patients enrolled in the study.
Even if a patient is considered ineligible by the investigators at the time of eligibility check after providing informed consent, and the subject registration form of the patient is not faxed to the sponsor, if the investigators later confirms that the patient meets the eligibility criteria, the investigators may again obtain consent for participation in the study from the patient and fax the subject registration form to the sponsor.

Figure 5-1 Patient Registration Procedure



5.1.3 Blinding

This is an open-label study.

5.1.4 Emergency Unblinding Procedure

Not applicable

5.2 Study Drug

5.2.1 Description

For the details of the study drug and its handling, see the "Investigator's Brochure" and "Study Drug Management Procedures."

1) Investigational substance code: AC220
2) Generic name (r-INN): Quizartinib
3) Content and dosage form: White film-coated tablets, each of which contains 20 mg AC220, or yellow film-coated tablets, each of which contains 30 mg AC220.

4) Lot number: Lot numbers are listed in the "Study Drug Management Procedures."

5.2.2 Labeling and Packaging

The packaging form and information displayed on the label of the study drug will be provided in the "Study Drug Management Procedures."
Thirty study drug tablets are packaged in a plastic bottle (for 1 patient).
The information displayed on the label is shown in "Table 5.2-1 Information Displayed on the Study Drug Label."

Table 5.2-1 Information Displayed on the Study Drug Label

Statement, "For clinical study"
Name of the study drug
Protocol number
Lot number of the study drug
Storage conditions
Statement, "Do not discard but store any unused study drug tablets; they will be collected later."
Name of the sponsor
Address of the sponsor

5.2.3 Preparation

All study drugs will be supplied as tablets that need no further preparation at the study centers.

5.2.4 Administration

5.2.4.1 Dose of the Study Drug

Quizartinib will be administered at an initial dose of 30 mg/day. For patients receiving strong CYP3A4 inhibitors, an initial dose of 20 mg/day will be used. Subsequently, whether or not to increase the initial dose of 30 mg/day to 60 mg/day or 20 mg/day to 30 mg/day will be determined on Day 16 of Cycle 1 and Day 1 of Cycle 2 (or thereafter) in accordance with "5.2.4.3 Criteria for Dose Increase of the Study Drug." If patients who achieve CR, CRp, or CRi after the start of treatment with the study drug and then subsequently relapse meet "5.2.4.3 Criteria for Dose Increase of the Study Drug," the dose of quizartinib may be increased in the same manner.
The dose of the study drug will be reduced in accordance with each of the criteria for dose reduction given in "5.4 Dose Interruptions and Reductions." If the dose is reduced due to QTcF prolongation, treatment for QTcF prolongation will be given in accordance

with "9.10.2 Measures Taken in Case of QTcF Prolongation."
In principle, central ECG assessment results will be used to make a decision on dose increase or reduction of the study drug. If it is necessary to urgently confirm the central assessment results on Day 15 of Cycle 1 or Day 1 of Cycle 2, etc., the study center should contact the Central ECG Reading Center and request immediate assessment (within 24 hours).

5.2.4.2 Regimen

Quizartinib will be orally administered once daily every morning. Treatment with quizartinib will be administered in 28-day cycles and continued until "5.7.1 Discontinuation Criteria for Treatment with the Study Drug" are met. The first dose of the study drug will be started, in principle, within 7 days of registration. If treatment with the study drug is started more than 7 days after registration, it should be confirmed again that the patient meets the eligibility criteria before the start of the first dose of the study drug.
If a patient vomits after taking a dose of the study drug, a replacement dose may not be given on the same day.
A patient who did not take the study drug at the usual hour of dosing (eg, forgot to take the dose) will be allowed to take the missed dose within 10 hours after the usual hour of dosing (for example, if the patient usually takes the drug at 7:00 or 8:00, he/she may take it by 18:00). In this case, the next dose of the study drug on the following day should be taken at least 12 hours after the time when the last dose was taken. If the patient does not take the missed dose by 10 hours after the usual hour of dosing, he/she should not take the study drug on that day and resume taking the drug on the following day. The patient may not take two doses at once on the day when the drug is resumed.

5.2.4.3 Criteria for Dose Increase of the Study Drug

If the patient's condition satisfies the following criteria on Day 16 of Cycle 1 or Day 1 of Cycle 2 (or thereafter), the dose of quizartinib will be increased according to Table 5.2-2.
A 12-lead ECG will be measured at least once weekly for the first 2 weeks after a dose increase to confirm the presence or absence of QTcF prolongation after the dose increase. When doing this, triplicate ECG recordings will be obtained. The dose of quizartinib should not exceed 60 mg/day throughout the study period (30 mg/day for patients concomitantly using strong CYP3A4 inhibitors).

Table 5.2-2 Method of Dose Increase of Quizartinib

Dose	One level Increased Dose
20 mg/day	30 mg/day
30 mg/day	60 mg/day
60 mg/day	No dose increase

Assessment criteria for dose increase on Day 16 of Cycle 1

Patients not concomitantly using strong CYP3A4 inhibitors:
The dose of quizartinib will be increased to 60 mg/day if all QTcF data (determined as the average of three measurements) taken by Day 15 of Cycle 1 are 450 ms or shorter.

Patients concomitantly using strong CYP3A4 inhibitors:
The dose of quizartinib will be increased to 30 mg/day if all QTcF data (determined as the average of three measurements) taken by Day 15 of Cycle 1 are 450 ms or shorter.
A list of CYP3A4 inhibitors is provided in Appendix 4.

If treatment with quizartinib is interrupted by Day 16 of Cycle 1, whether to increase the dose or not will be determined in accordance with the following criteria.

- Interruption of treatment for 2 days or shorter: The dose may be increased on Day 16 of Cycle 1.
- Interruption of treatment for 3 to 6 days: Consult with the sponsor's medical monitor etc. and assess whether to increase the dose or not on Day 16 of Cycle 1.
- Interruption of treatment for 7 days or longer: The dose will not be increased on Day 16 of Cycle 1. Decide whether to increase the dose or not on Day 1 of Cycle 2 or later.

Assessment criteria for dose increase on Day 1 of Cycle 2 or later

For patients who have not achieved CR, CRp, or CRi after at least 1 cycle of treatment with quizartinib* and whose condition before the decision on dose increase satisfies the following requirements, the dose of quizartinib will be increased.

- Absence of Grade 3 or more severe treatment-related non-hematological toxicity
- 60 ms or shorter increase in QTcF interval from baseline
- Absence of hypoplastic bone marrow upon the decision of a dose increase

* At least 1 cycle of treatment with quizartinib: Treatment with quizartinib is given for at least 13 consecutive days

For patients who have relapsed after achieving CR, CRp, CRi, or PR, and satisfy the assessment criteria for dose increase on Day 1 of Cycle 2 or later, the dose of quizartinib may be increased. The dose will be increased to 60 mg/day if strong CYP3A4 inhibitors are not concomitantly used, and to 30 mg/day if strong CYP3A4 inhibitors are concomitantly used.

5.2.5 Storage

The study drug manager will store and manage the study drug at 25°C or lower without freezing.

5.2.6 Drug Accountability

After receiving the delivered study drug, the study drug manager or designee will check the quantity and condition of the study drug and confirm the appropriateness of the labeling as well as the expiry date of the study drugs etc. In addition, the investigator or designee shall contact the sponsor as soon as possible if there is a problem with the study drug.

The study drug will be managed using the Drug Accountability Record. The Accountability Record must be updated, and should contain such information as the date of receipt of the study drug, the quantity of the received study drug, patients supplied with the study drug (identification number, or if applicable, supply number), date of supply of the study drug, quantity supplied and residual quantity, and the signed initials and seal of the person who supplied the study drug. At the end of the study, the investigator or designee must prepare the final version of the study drug management-related record, and submit it to the sponsor.

Other procedures related to study drug management and collection will be performed in accordance with the “Study Drug Management Procedures.”

5.3 Control Treatment

Not applicable

5.4 Dose Interruptions and Reductions

If any of the criteria in Section 5.4.1 to Section 5.4.4 apply, treatment with quizartinib will be interrupted or the dose of quizartinib will be reduced. The dose of quizartinib will be reduced by one level at a time according to Table 5.4-1. If quizartinib is administered at a dose of 20 mg/day, a further dose reduction is not allowed.

Table 5.4-1 Method of Dose Reduction of Quizartinib

Dose	One level Reduced Dose
60 mg/day	30 mg/day
30 mg/day	20 mg/day
20 mg/day	No dose reduction

5.4.1 QTcF Prolongation

In case of QTcF prolongation, the dose will be reduced in the following manner.

Table 5.4-2 Criteria for Dose Interruption and Reduction When QTcF Prolongation Occurs during Treatment with Quizartinib at 30 mg/day or 60 mg/day

CTCAE Grade	Method of Dose Reduction
Grade 2	• Reduce the dose by one level. It is not necessary to interrupt treatment. • The dose may be increased to the dose before dose reduction if QTcF prolongation recovers to Grade 1 or less severe after treatment at the reduced dose for at least 28 days.
Grade 3	• Interrupt quizartinib treatment for a maximum of 14 days. • Resume quizartinib treatment at a one level reduced dose, relative to the dose immediately before the interruption, if the increase in QTcF interval from baseline is 30 ms or shorter or the QTcF interval recovers to 450 ms or shorter within 14 days after the onset. • Do not increase the dose after resumption of quizartinib treatment.
Grade 4	Discontinue quizartinib treatment.

For the treatment of QTcF prolongation, "9.10.2 Measures Taken in Case of QTcF Prolongation" should be followed.

Table 5.4-3 Criteria for Dose Interruption and Reduction When QTcF Prolongation Occurs during Treatment with Quizartinib at 20 mg/day

CTCAE Grade	Method of Dose Reduction
Grade 2	• Interrupt quizartinib treatment for a maximum of 14 days. • Resume quizartinib treatment at a dose of 20 mg/day if QTcF prolongation recovers to Grade 1 or less severe.
Grade 3	[If strong CYP3A4 inhibitors are concomitantly used] • Interrupt quizartinib treatment for a maximum of 14 days. • Resume quizartinib treatment at a dose of 20 mg/day if the increase in QTcF interval from baseline is 30 ms or shorter or the QTcF interval recovers to 450 ms or shorter within 14 days after the onset, and the concomitant use of strong CYP3A4 inhibitors is discontinued. • Do not increase the dose after resumption of quizartinib treatment. [If strong CYP3A4 inhibitors are not concomitantly used] • Discontinue quizartinib treatment.
Grade 4	Discontinue quizartinib treatment.

For the treatment of QTcF prolongation, "9.10.2 Measures Taken in Case of QTcF Prolongation" should be followed.

5.4.2 Non-hematological Toxicity

If a quizartinib-related Grade 3 or more severe non-hematological toxicity does not improve to Grade 2 or less severe, and it persists for at least 48 hours, treatment with quizartinib should be interrupted for a maximum of 14 days when quizartinib has been administered at a dose of 30 mg/day or 60 mg/day. If the toxicity recovers to Grade 1 or less severe within 14 days after the onset, treatment with quizartinib may be resumed at a reduced dose. When quizartinib is administered at a dose of 20 mg/day, treatment with quizartinib should be discontinued.

5.4.3 Bone Marrow Depression

If all of the following criteria apply in patients achieving CRp or CRi, dose reduction should be considered in the opinion of the investigators. If an improvement in bone marrow depression is not observed even after dose reduction, interruption of treatment for a maximum of 14 days should be considered (also when quizartinib is administered at a dose of 20 mg/day in patients meeting all of the following criteria, interruption of treatment should be considered).

- Completion of 1 or more cycles of treatment with quizartinib
- Platelet count of less than 100 000/mm^3 and neutrophil count of 1000/mm^3 or less
- Less than 5% blasts in the bone marrow
- Absence of extramedullary lesions

If an improvement in bone marrow depression is observed within 14 days after interruption of treatment, treatment with quizartinib may be resumed at the dose before interruption of treatment. If the dose before interruption of treatment is 20 mg/day, the treatment may be resumed at 20 mg/day.

5.4.4 If Concomitant Use of Strong CYP3A4 Inhibitors Is Started during the Study Period

If concomitant use of strong CYP3A4 inhibitors is started during the study period, the dose of quizartinib will be reduced by one level. If concomitant use of strong CYP3A4 inhibitors is discontinued, quizartinib may be administered at the dose used before dose reduction after a 7-day washout.

5.4.5 Dose Increase after Dose Reduction

The dose of quizartinib will be increased by one level at a time in patients whose dose has once been reduced. However, if the dose of quizartinib is reduced associated with

Grade 3 QTcF prolongation, the dose may not be increased. If the dose of quizartinib is reduced associated with Grade 2 QTcF prolongation, the dose may be increased to the dose before dose reduction if QTcF prolongation recovers to Grade 1 or less severe after treatment at a reduced dose for at least 28 days.
If the dose of quizartinib is reduced due to AEs, the dose must not be increased unless the concerned AE recovers to Grade 1 or less severe. If the dose of quizartinib is reduced because concomitant use of a strong CYP3A4 inhibitor is started during the study, quizartinib may be administered at the dose before dose reduction after a 7-day washout when the concomitant use of the strong CYP3A4 inhibitor is discontinued.

5.5 Method of Assessing Treatment Compliance

The investigators will evaluate the patient's treatment compliance with the study drug based on the information in the dosing diary filled out by the patients and the number of tablets returned. Administration of the study drug will be recorded in the case report form (CRF)/Drug Accountability Record. If there are no returned tablets, the investigators should ask the patient whether any tablets were disposed of, rather than taken orally.
As the information on administration of the study drug, the dose of the study drug, date and time of administration, start date of treatment, date of discontinuation of treatment, date of interruption of treatment, date of resumption of treatment, reason for interruption of treatment, etc. will be clearly documented in the CRF.

5.6 Concomitant Medications

5.6.1 Investigation Items

All concomitant drugs and other therapies than the study drug that are used and transfusions introduced during the period from the day of the first dose of the study drug to the day of post-treatment observation will be recorded in the CRF. For concomitant drugs or therapies, or transfusion that is newly started after the day following the last dose of the study drug, those used only for the treatment of AEs will be recorded in the CRF. Concerning the details of the items to be entered, refer to Section 6.2.

5.6.2 Prohibited Concomitant Drugs, Restricted Concomitant Drugs, and Drugs to Be Coadministered with Care

5.6.2.1 Prohibited Concomitant Drugs

The drugs listed below should not be used concomitantly with the study drug from the

day of informed consent to the study through the day of post-treatment observation. It is, however, allowed to concomitantly use hydroxycarbamide at doses of up to 2 g/day only during the period from 14 days before the first dose of quizartinib to 4 days after the start of treatment with quizartinib. If hydroxycarbamide has been used at least 15 days before the start of the first dose of quizartinib, the first dose of quizartinib may be started with a 1-day washout.

1) Antiarrhythmic drugs, antibacterial, antifungal, psychotropic, and other drugs that may potentially prolong the QT/QTc interval (excluding medically unavoidable cases in the opinion of the investigators)
2) Strong or moderate CYP3A4 inducers
3) Crude drugs and food products with CYP3A4-inhibiting or -inducing properties (eg, foods and beverages containing St. John's wort or grapefruit)
4) Anticancer treatments other than quizartinib (Concomitant use of hydroxycarbamide during the aforementioned period is allowed.)
5) Investigational drugs other than quizartinib, and investigational devices

5.6.2.2 Drugs to Be Coadministered with Care

The following points should be noted during the period from the day of informed consent to the day of post-treatment observation.

- During treatment with quizartinib, use of substrates of P-glycoprotein should be avoided as far as possible.
- Concomitant use of strong CYP3A4 inhibitors is not prohibited, but should be avoided because it is required to start treatment with quizartinib at a reduced dose. Moderate or weak CYP3A4 inhibitors (fluconazole etc.) may be used concomitantly without reducing the dose of quizartinib.

<Rationale>

These specifications are provided for proper safety evaluation of quizartinib.
Quizartinib and AC886 are mainly metabolized by CYP3A4. If the need arises to use drugs that may potentially prolong the QT/QTc interval or strong or moderate CYP3A4 inducers by necessity for the prevention or treatment of infection during the study, concomitant use of these drugs with quizartinib should be avoided.
In addition, in vitro data indicate that quizartinib inhibits P-glycoprotein. For this reason, concomitant use of quizartinib with substrates of P-glycoprotein should be avoided as far as possible. Concomitant use of quizartinib with P-glycoprotein

substrates may increase the blood concentrations of the P-glycoprotein substrates.

5.7 Subject Withdrawal/Discontinuation

5.7.1 Discontinuation Criteria for Treatment with the Study Drug

If any of the following criteria apply, the investigators should immediately discontinue treatment with the study drug and proceed to the post-treatment observation period.

1) Overt disease progression is observed.
2) Grade 4 QTcF prolongation is observed.
3) The investigators decide that continued treatment with the study drug is no longer beneficial to the patient based on AEs and the results of laboratory test values.
4) LVEF is less than 45%.
5) The investigators decide to introduce HSCT.
6) Treatment with quizartinib is interrupted for longer than 14 days.
7) The patient is found to deviate from the inclusion criteria or fit the exclusion criteria after registration.
8) Pregnancy is found after registration.
9) The sponsor decides to discontinue the study.
10) The patient requests for withdrawal from treatment with the study drug.
11) Other circumstances why the study cannot be continued in the opinion of the investigators

If treatment with the study drug is discontinued, the investigators should take appropriate actions for the patients, and then perform tests/assessments specified in "6.3 Procedures When Treatment with the Study Drug Is Discontinued," and record the obtained information in the CRF. The date of discontinuation of treatment with the study drug and the reason for discontinuation will also be recorded in the CRF. The date of discontinuation of treatment with the study drug is not the date when the AE leading to discontinuation occurs, but the date when the investigators determine discontinuation of the treatment.

5.7.2 Reasons for Discontinuation during the Post-treatment Observation Period and the Follow-up Period

If the study is discontinued during the patient's post-treatment observation period or the follow-up period for the following reasons, the date of discontinuation and the reason for discontinuation will be recorded in the CRF.

1) The patient died.
2) The patient requests for withdrawal from the study during the post-treatment observation period or the follow-up period.
3) The patient is lost to follow-up.
4) The sponsor decides to discontinue the study.
5) Other

5.7.3 Withdrawal Procedures

If a patient is withdrawn from the study, the investigators will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last administration and the reason for withdrawal.
If the patient is withdrawn due to an AE, the investigators will follow the patient as far as possible until the AE has resolved or stabilized.
All patients who are withdrawn from the study should complete protocol-specified withdrawal procedures.

6. STUDY PROCEDURES

Study procedures specified in the protocol are shown in "Table 6-1 Schedule of Study Procedures."
In the study, the period from the day of informed consent through the last day of the follow-up period is defined as the "study period" for each patient. However, if a patient has difficulty to attend the follow-up at the study center for reasons including transfer to another hospital or he/she refuses to visit the study center after the final dosing of quizartinib, then the study period for the patient will be terminated on the relevant day.

Table 6-1 Schedule of Study Procedures

	Screening (≤ 14 Days before Registration)	Cycle 1				Cycle 2		Cycle 3	Cycle 4 and Thereafter	At Withdrawal	Post treatment Observation	Follow up
		Day 1	Day 2 and 8	Day 15	Day 16	Day 1	Day 15	Day 1	Day 1		30 Days after the Last Dose	
Acceptable limit (unit: days)			Day 2: Scheduled Day Day 8: ±1	±1	(Must Be the Day Following Day 15)	±3	±1	±3	±3	3 to +7	+15	Every 3 Months
Informed consent	●											
FLT3 ITD test	●*1											
Administration of quizartinib (at the study center)		●*2	●*2	●*2	●*2	●*2	●*2	●*2	●*2			
Medical history/complications	●											
Vital sign measurement	●	●	●	●		●	●	●	●	●	●	
ECOG PS/body weight	●	●				●		●	●	●	●	
Height	●											
Laboratory tests (hematology, blood chemistry, urinalysis)	●	●*3	●*3	●*3		●*3	●*3	●*3	●*3	●	●	
Pregnancy test	●											
HIV antibody	●*4											
12 lead ECG	●*5	●*5	●*5	●*5		●*5		●*5	●*5	●*5		
X ray examination	●	○ (as needed)										
MUGA scan or echocardiography	●*6	○ (as needed)										
Assessment of bone marrow findings (tumor assessment)	●*7					●*7		●*7	●*7	●*7		
Measurement of drug concentrations		●*8	●*8	●*8	●*8	●*8		●*8				
Inhibitory activity on phosphorylated FLT3 and c Kit proteins		●*9	●*9	●*9		●*9						
AEs	●*10											
Assessment of concomitant drugs and therapies		●										
Investigation of survival status Other leukemia treatment etc.											●	●

1) FLT3 ITD levels will be measured using a bone marrow specimen or peripheral blood. The collected bone marrow specimen or peripheral blood will immediately be submitted to the specimen collection agency.
2) Quizartinib will be administered on Days 1, 2, 8, 15, and 16 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of Cycle 3, and Day 1 of Cycle 4 and subsequent cycles at the study center. Quizartinib may be administered at home on the other days.

3) To be measured before administration of the study drug.
4) To be performed within 120 days before registration.
5) ECG will be measured three times (triplicate ECGs) at each of the following time points. Triplicate ECGs will be obtained at least once weekly for the first 2 weeks after increasing the dose of quizartinib to carefully confirm the QTcF interval.
   Screening, Day 1 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 2 and Day 8 of Cycle 1 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 1 of Cycle 2 ([if the dose of quizartinib is increased on Day 16 of Cycle 1]: before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug, [if the dose of quizartinib is not increased on Day 16 of Cycle 1]: before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 1 of Cycle 3 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), and Cycle 4 thereafter (before administration of the study drug on Day 1 of each cycle)
6) A multiple gated acquisition (MUGA) scan or echocardiography must be performed at screening except in case LVEF is 45% or more within 1 month before registration.
7) It is desirable to assess bone marrow findings with specimens obtained by both bone marrow aspiration and biopsy; however, bone marrow biopsy may be skipped if the antitumor effect can be evaluated adequately only by bone marrow aspiration in the opinion of the investigators. Assessment of bone marrow findings will be performed at screening (it is desirable to obtain the specimen within 14 days before registration; however, the specimen collected before the time may be used with the consent of the medical monitor etc.), on Day 1 of Cycle 2 and subsequent cycles, at the time of discontinuation of the study, and other time points if assessment is considered necessary by the investigators. For patients achieving CR, CRp, or CRi, bone marrow findings will be assessed every 3 cycles.
8) A plasma specimen for pharmacokinetic measurement will be collected at the following specified time points. If ECG and blood collection for pharmacokinetics (PK) are scheduled at the same time, blood collection for PK will be performed immediately after the end of ECG.
   Day 1 of Cycle 1 (before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug), Day 8 of Cycle 1 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug), Day 1 of Cycle 2 ([if the dose of quizartinib is increased on Day 16 of Cycle 1]: before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug, [if the dose of quizartinib is not increased on Day 16 of Cycle 1]: before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), and Day 1 of Cycle 3 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug).
9) A specimen for measurement of inhibitory activity on phosphorylated FLT3 and c Kit proteins will be collected at the following specified time points.
   Day 1 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 8 of Cycle 1 (before administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug), and Day 1 of Cycle 2 (before administration of the study drug).
10) Only information on SAEs will be collected during the period from the day of informed consent to before the first dose of the study drug.

6.1 Procedures to Be Performed before Patient Registration

The procedures listed below will be performed, and the results will be recorded in the CRF.

For each assessment item, data obtained before informed consent within the allowable time limits for each item may also be used.

If the study drug is started on Day 7 or later if the day of registration is defined as Day 0, the patient's eligibility should be assessed again on the preceding day or the start day (before dosing) of treatment with the study drug.

If 12-lead ECG measurement, vital sign measurement, and blood collection for laboratory tests etc. are scheduled on the same day, blood collection will be performed after 12-lead ECG and vital sign measurements.

1) Items to be collected or assessed after informed consent is obtained but before the start of the patient registration procedure
   - If informed consent for tests for mutations of the FLT3-ITD gene is obtained before obtaining informed consent for participation in the study, the date of informed consent
   - Date of informed consent for participation in the study
   - Presence or absence of mutations of the FLT3-ITD gene and FLT3-ITD assessment result
     - Mutations of the FLT3-ITD gene will be tested at Navigate BioPharma using peripheral blood or bone marrow liquid after informed consent. Patients who have not previously undergone mutation tests of the FLT3-ITD gene at any testing company may be tested for mutations of the FLT3-ITD gene at SRL, if necessary, and their eligibility for the study may be assessed without having to wait for the result of the test at Navigate BioPharma.
     - If the test result of Navigate BioPharma is found to be different from the test result of the hospital or SRL after registration based on the result of the previous FLT3-ITD mutation test performed at the testing company or SRL, the investigators will decide whether to continue treatment with the study drug or not for the concerned patient. In other words, even if the test result of Navigate BioPharma is negative, if continued treatment with the study drug may be beneficial to the patient in the opinion of the investigators, treatment with the study drug may be continued.
   - Subject identification code

- Date of birth
- Sex
- Race
- Height
- Eligibility
- Medical history and complications
  Assess the presence or absence of medical history and complications, presence or absence of symptoms on the day of the first dose of the study drug (if any symptoms are present, it should be handled as a complication), findings, and the diagnosis.
  Only the medical history that needs to be reported in the opinion of the investigators, will be listed.
- Information on the underlying disease (AML)
  Collect data on the date of the first diagnosis, the WHO classification, and the date of relapse.
- Prior therapy:
  Collect data on the following items:
  - Medications for AML: Presence or absence, drug name, stop date, best response, number of courses
  - Radiation therapy for AML: Presence or absence, purpose, location, stop date, best response
  - HSCT: Presence or absence, details, date of transplantation
  - Others: Presence or absence, details, stop date
- Confirmation of serious adverse events (SAEs)
  Information on SAEs that occur during the period from informed consent to before the first dose of the study drug will be collected. Collection of information on nonserious AEs is not required.

2) Items to be collected or assessed between Day 14 and Day 0 (day of registration) (collected or assessed on a day as close as possible to the day of registration)
   - Vital sign measurement
     Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured in the supine position after a 5-minute rest.
   - Body weight
   - ECOG PS assessment

The patient's PS will be assessed according to the criteria provided in Appendix 2.

- 12-lead ECG (including QTcF assessment)
  A 12-lead ECG will be performed in triplicate in the supine position after a 10-minute rest. The measurements will be performed at approximately 3- to 5-minute intervals.
- Laboratory tests

	Laboratory Parameter
Hematology test	Red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin, hematocrit, white blood cell count, white blood cell differential count (neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelet count, and PT INR
Blood chemistry test	Total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, ALP, γ GT, LDH, lipase, BUN, serum creatinine, creatine kinase, uric acid, glucose, electrolytes (K, Na, Cl, Ca, P, Mg), CRP, total cholesterol,* LDL,* HDL,* and triglyceride*
Urinalysis	Specific gravity, pH, occult blood, glucose, protein, bilirubin, and ketone bodies

* These parameters will be measured only at screening and at the time of discontinuation (no dietary restrictions).

- Assessment of bone marrow findings
  Assessment will be made based on the bone marrow findings and peripheral blood results (neutrophil count, platelet count, and presence or absence of blasts) in accordance with "7.1 Definition of Efficacy Endpoints." Even if a bone marrow test is not performed within 14 days (Day 14) before registration (day of registration is regarded as Day 0), if consent of the medical monitor etc. is obtained, the concerned data may be used for assessment of bone marrow findings.
- Chest X-ray (Posterior or lateral radiographs will be taken, as necessary.)
- Pregnancy test
  A urine or serum pregnancy test will be performed in female patients.
  A pregnancy test is not necessary in women who have been amenorrheic for at least 2 years after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the CRF.
  A pregnancy test must be performed in women who have been amenorrheic for at least 2 years for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.
- A MUGA scan or echocardiography (however, excluding cases of LVEF of 45%

or more based on the result of the test performed within 1 month after the screening test)

3) Items to be collected or assessed between Day 120 and Day 0 (day of registration)
   - HIV antibody

6.2 Procedures during the Study Conduct Phase

The procedures listed below will be performed, and the results will be recorded in the CRF.

The details of the procedures are the same as those described in "6.1 Procedures to Be Performed before Patient Registration."

If 12-lead ECG measurement, vital sign measurement, and blood collection for laboratory tests etc. are scheduled on the same day, blood collection will be performed after 12-lead ECG and vital sign measurements.

1) Confirmation of the status of administration of the study drug
   - Presence or absence of administration
   - Dates of doses administered
   - Timing of dosing
   - Amount of dose administered (mg/day)
   - Presence or absence of interruption and dose reduction (if present, the details and reason for it)

2) Vital sign measurement

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre dose
	Day 2	Pre dose
	Day 8 (±1 day)	Pre dose
	Day 15 (±1 day)	Pre dose
Cycle 2	Day 1 (±3 days)	Pre dose
	Day 15 (±1 day)	Pre dose
Cycle 3 and thereafter	Day 1 (±3 days)	Pre dose

3) Body weight

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre dose
Cycle 2 and thereafter	Day 1 (±3 days)	Pre dose

4) ECOG PS assessment

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre dose
Cycle 2 and thereafter	Day 1 (±3 days)	Pre dose

5) 12-lead ECG

A 12-lead ECG will be performed in triplicate (triplicate ECG) in the supine position after a 10-minute rest. The measurements will be performed at approximately 3- to 5-minute intervals. For the details, refer to "9.10.1 Measurement Method."

It should be noted that the measurement time points are different if the dose of quizartinib is increased or not increased on Day 16 of Cycle 1, as shown below.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre dose 2 hours (±10 minutes) post dose 4 hours (±10 minutes) post dose 6 hours (±10 minutes) post dose
	Day 2	Pre dose (24 hours post dose on Day 1) 2 to 4 hours post dose
	Day 8 (±1 day)	Pre dose 2 to 4 hours post dose
	Day 15 (±1 day)	Pre dose 2 hours (±10 minutes) post dose 4 hours (±10 minutes) post dose 6 hours (±10 minutes) post dose
Cycle 2	Day 1 (±3 days) If the dose of quizartinib is increased on Day 16 of Cycle 1	Pre dose 2 hours (±10 minutes) post dose 4 hours (±10 minutes) post dose 6 hours (±10 minutes) post dose
	If the dose of quizartinib is not increased on Day 16 of Cycle 1	Pre dose 2 to 4 hours post dose
Cycle 3	Day 1 (±3 days)	Pre dose 2 to 4 hours post dose
Cycle 4 and thereafter	Day 1 (±3 days)	Pre dose

A 12 lead ECG will be performed at least once weekly for 2 weeks after increasing the dose of quizartinib to carefully confirm the QTcF interval.

6) Laboratory tests

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre dose
	Day 2	Pre dose
	Day 8 (±1 day)	Pre dose
	Day 15 (±1 day)	Pre dose
Cycle 2	Day 1 (±3 days)	Pre dose
	Day 15 (±1 day)	Pre dose
Cycle 3 and thereafter	Day 1 (±3 days)	Pre dose

7) Assessment of bone marrow findings

Assessment will be made based on the bone marrow findings and peripheral blood results (neutrophil count, platelet count, and presence or absence of blasts) in accordance with "7.1 Definition of Efficacy Endpoints."

It is desirable to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of quizartinib can be assessed adequately using specimens obtained by bone marrow aspiration alone, bone marrow biopsy may be omitted.

Cycle 2	Day 1	On the specified day (±3 days)
Cycle 3	Day 1	On the specified day (±3 days)
Cycle 4 and thereafter	Day 1	On the specified day (±3 days)

After achievement of CR, CRi, or CRp, the antitumor effect will be assessed every 3 cycles until the appearance of leukemic blasts in the peripheral blood. Assessment will be performed at other time points if necessary.

8) Confirmation of concomitant drugs and therapies, and transfusion

- Concomitant drugs and therapies

  The following information on concomitant drugs and therapies other than the study drug, which are used during the period from the day of the first dose of the study drug to the day of post-treatment observation will be confirmed. As for concomitant drugs or therapies that are newly started after the day following the last dose of the study drug, those used only for the treatment of AEs will be confirmed.

  - Name of drug (therapy), dose, unit, mode of administration, frequency
  - Start and stop dates of drug (therapy)
  - Reason for use (application)

  The following items do not have to be recorded in the CRF unless a relationship of them with the AEs occurring during study participation cannot be ruled out:

  - Antiseptic solutions
  - Heparin for heparin lock flush
  - Test or procedural agents used for tests including bone marrow aspiration or biopsy

- Transfusion

  The following information on transfusion that is introduced during the period from the day of the first dose of the study drug to the day of post-treatment

observation will be confirmed. As for transfusion that is newly started after the day following the last dose of the study drug, the one used only for the treatment of AEs will be confirmed.

- Type of blood products (whole blood, red blood cells, plasma, platelets, others)
- Start date, end date, amount of use (unit)
- Reason for use

9) Monitoring of AEs
10) Collection of specimens for pharmacokinetic assessment and the biomarker study
Refer to "6.8 Pharmacokinetics," "6.9 FLT3-ITD Mutation Test," and "6.10 Biomarker Study."

6.3 Procedures When Treatment with the Study Drug Is Discontinued

The procedures listed below will be performed on the day when the investigators decide discontinuation of treatment with the study drug (within 3 to +7 days).
The details of the procedures are the same as those described in "6.1 Procedures to Be Performed before Patient Registration" and "6.2 Procedures during the Study Conduct Phase."

- Date of discontinuation of treatment with the study drug and reason for discontinuation
- Vital sign measurement
- Body weight
- ECOG PS assessment
- 12-lead ECG
- Laboratory tests
- Assessment of bone marrow findings (It is desirable to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of quizartinib can be assessed adequately using specimens obtained by bone marrow aspiration alone, bone marrow biopsy may be omitted.)
- Confirmation of concomitant drugs and therapies, and transfusion
- Monitoring of AEs
- Confirmation of the status of administration of quizartinib

6.4 Procedures during the Post-treatment Observation Period

The procedures listed below will be performed at day 30 (+15 days) when the day of the last dose of the study drug is set day 0. The post-treatment observation will be performed before the start of post treatment, if it is initiated.

The day when all the procedures have been completed is defined as the day of completion of the post-treatment observation period.

If any AEs have not resolved by the day of completion of the post-treatment observation period, follow-up should be continued as far as possible until the AE is resolved or reduced.

The details of the procedures are the same as those described in "6.1 Procedures to Be Performed before Patient Registration" and "6.2 Procedures during the Study Conduct Phase."

- Vital sign measurement
- Body weight
- ECOG PS assessment
- Laboratory tests
- Confirmation of survival (the last date of confirming survival) or death (the date of death)
- Confirmation of concomitant drugs and therapies, and transfusion
- Monitoring of AEs
- Post treatment for AML after discontinuation of treatment with quizartinib
- Presence or absence of relapsed AML, and if present, the date of relapse

6.5 Post Treatment

Treatment used for AML after the day of the last dose of the study drug (eg, HSCT, chemotherapy, immunotherapy, radiation therapy, and others) is defined as "post treatment."

Post treatment should not be started before the day of completion of the post-treatment observation period as far as possible. If post treatment is started by necessity before completion of the post-treatment observation period, the name and start date of the post treatment will be recorded in the CRF.

6.6 Follow-up

The following information will be confirmed every 3 months after assessment during the post-treatment observation period (confirmation by phone is allowed).

- Investigation of survival status
- Post treatment for AML after discontinuation of treatment with quizartinib
- Presence or absence of relapsed AML, and if present, the date of relapse

6.7 Definition of the Study Period

The study period for each patient is from the time of informed consent to the end of the follow-up assessment.

6.8 Pharmacokinetics

A total of 2 mL of blood will be drawn, well mixed by inverting the tube, and centrifuged (≥ 15°C, 1500 g, 10 minutes) within 20 minutes after blood collection. The obtained plasma will be stored frozen between 90°C and 70°C. The specimens in a frozen state will be submitted to the agency contracted by the sponsor to collect the specimens. Details including the handling of specimens will be specified in separate procedures.
The date and time of blood collection will be recorded in the CRF.
If 12-lead ECG measurement, vital sign measurement, and blood collection are scheduled at the same time, blood collection will be performed after 12-lead ECG and vital sign measurements.

Table 6.8-1 Blood Collection Points for Pharmacokinetic Assessment

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Limit)
Cycle 1	Day 1	Pre dose (60 minutes) 1 hour (±30 minutes) post dose 2 hours (±30 minutes) post dose 4 hours (±30 minutes) post dose 6 hours (±30 minutes) post dose 24 hours post dose (within 3 hours pre dose on Day 2 of Cycle 1)
	Day 8 (±1 day)	Pre dose (60 minutes) 2 to 4 hours post dose
	Day 15 (±1 day)	Pre dose (60 minutes) 1 hour (±30 minutes) post dose 2 hours (±30 minutes) post dose 4 hours (±30 minutes) post dose 6 hours (±30 minutes) post dose 24 hours post dose (within 3 hours pre dose on Day 16 of Cycle 1)
Cycle 2	Day 1 (±3 days) If the dose of quizartinib is increased on Day 16 of Cycle 1	Pre dose (60 minutes) 1 hour (±30 minutes) post dose 2 hours (±30 minutes) post dose 4 hours (±30 minutes) post dose 6 hours (±30 minutes) post dose 24 hours post dose (within 3 hours pre dose on Day 2 of Cycle 2)
	If the dose of quizartinib is not increased on Day 16 of Cycle 1	Pre dose (60 minutes) 2 to 4 hours post dose
Cycle 3	Day 1 (±3 days)	Pre dose (60 minutes) 2 to 4 hours post dose

6.9 FLT3-ITD Mutation Test

To investigate the presence or absence of mutations of the FLT3-ITD gene, 2 mL of bone marrow liquid or 4 mL of peripheral blood (1 mL of bone marrow liquid or 2 mL of peripheral blood if the measurement is not performed at SRL) will be collected after obtainment of informed consent, but before registration, and the specimen will immediately be submitted to the specimen collection agency contracted by the sponsor under the designated temperature conditions.

6.10 Biomarker Study

6.10.1 Plasma Inhibitory Activity of Quizartinib on Phosphorylated FLT3 and c-Kit Proteins

A total of 2 mL of blood will be drawn, well mixed by inverting the tube, and centrifuged (≥ 15°C, 1500 g, 10 minutes) within 20 minutes after blood collection. The obtained plasma will be stored frozen between 90°C and 70°C. The specimens in a frozen state will be submitted to the agency contracted by the sponsor to collect the specimens. Details including the handling of specimens will be specified in separate procedures.

The date and time of blood collection will be recorded in the CRF.
If 12-lead ECG measurement, vital sign measurement, and blood collection are scheduled at the same time, blood collection will be performed after 12-lead ECG and vital sign measurements.

Table 6.10-1 Blood Collection Points for Plasma Inhibitory Activity

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Limit)
Cycle 1	Day 1	Pre dose (60 minutes) 2 hours (±30 minutes) post dose 4 hours (±30 minutes) post dose 6 hours (±30 minutes) post dose
	Day 8 (±1 day)	Pre dose (60 minutes)
	Day 15 (±1 day)	Pre dose (60 minutes)
Cycle 2	Day 1 (±3 days)	Pre dose (60 minutes)

7. EFFICACY ASSESSMENTS

The antitumor effect of quizartinib will be assessed based on bone marrow findings and neutrophil and platelet counts in the peripheral blood, as specified in "7.1 Definition of Efficacy Endpoints."

7.1 Definition of Efficacy Endpoints

The efficacy endpoints are defined in Table 7.1-1.

Table 7.1-1 Definition of Efficacy Endpoints

Complete remission (CR)	For patients to be classified as CR, they must achieve a morphologic leukemia free state, must have less than 5% blasts in the bone marrow (no Auer rods), a neutrophil count of 1000/mm^3 or more, and a platelet count of 100 000/mm^3 or more, must be independent of red blood cell (RBC) and platelet transfusions (defined as 4 weeks without RBC transfusion and 1 week without platelet transfusion), and may not have extramedullary leukemia.
CR with incomplete hematological recovery (CRi)	For patients to be classified as CRi, they must fulfill all the criteria for CR, except for incomplete hematological recovery with residual neutropenia of less than 1000/mm^3. Platelet recovery status and RBC and platelet transfusion independence are not required.
CR with incomplete platelet recovery (CRp)	For patients to be classified as CRp, they must fulfill all the criteria for CR, except for incomplete platelet recovery (< 100 000/mm^3).
Partial remission (PR)	For patients to be classified as PR, they must have bone marrow regenerating normal hematopoietic cells, no or minimal residual blast cells in the peripheral blood, a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate, and total marrow blasts between 5% and 25% inclusive. Whether the neutrophil count or platelet count has recovered or not, or whether erythrocyte or platelet transfusion has been performed or not, will not be taken into consideration.
No response (NR)	NR is defined as a condition not reaching any of CR, CRi, CRp, or PR.
Unknown	No assessment is made after baseline.
Composite CR rate (CRc rate)	Composite CR rate (CRc rate) is defined as the proportion of patients whose best response is CR, CRi, or CRp.
Response rate	Response rate is defined as the proportion of patients whose best response is CR, CRi, CRp, or PR.
Relapse	Relapse after CR, CRi, or CRp: Defined as the reappearance of leukemic blasts in the peripheral blood or an increase in the percentage of blasts in the bone marrow aspirate to 5% or more, or the reappearance or new appearance of extramedullary leukemia. Relapse after PR: Defined as the reappearance of significant numbers of blasts in the peripheral blood or an increase in the percentage of blasts in the bone marrow aspirate to more than 25%, or the reappearance or new appearance of extramedullary leukemia.

7.2 Best Response

Best response is defined as the best measured response over all response assessments (CR, CRp, CRi, PR, NR, or Unknown) at all time points after the first dose of the study drug. The best response is presented as CR, CRp, CRi, PR, NR, or Unknown in descending order of efficacy.

7.3 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the CRc rate. The CRc rate is defined as

the proportion of patients whose best response is CR, CRp, or CRi.

7.4 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows.

- Best response
- Response rate
- Overall survival (time from registration to death)
- Event-free survival (time from registration to progression, relapse, or death, whichever occurs first)
- Leukemia-free survival (time from first achievement of CRc to relapse or death, whichever occurs first)
- Transplantation rate (proportion of patients who start HSCT immediately after the end of treatment with the study drug without receiving other treatment for AML)

7.5 Appropriateness of Selected Efficacy Endpoints

This study will be conducted to evaluate the efficacy of quizartinib in Japanese patients with FLT3-ITD positive relapsed or refractory AML. The reasons why the CRc was chosen as the primary efficacy endpoint are as follows: Prolonged OS has been reported in patients achieving CRc compared with patients failing to achieve CRc in the study in patients with relapsed or refractory AML,[15)] and achievement of CRc in Japanese patients with relapsed or refractory AML allows them to undergo HSCT, which is expected to provide prolongation of OS.

8. PHARMACOKINETIC/BIOMARKER ASSESSMENTS

The following items will be measured to evaluate the pharmacokinetics of quizartinib and quizartinib-related biomarkers.

8.1 Pharmacokinetic Endpoints

The pharmacokinetic parameters listed below will be calculated from the plasma concentrations of quizartinib and its active metabolite AC886 using a model independent approach.

Day 1 of Cycle 1: Cmax, Tmax, AUCtau

Day 15 of Cycle 1 and Day 1 of Cycle 2 (if the dose of quizartinib is increased on Day 16 of Cycle 1): Cmax,ss, Ctrough, Tmax,ss, AUCtau,ss

The details of the method of calculation of pharmacokinetic parameters are specified in

the Statistical Analysis Plan.

8.1.1 Amount and Time Points of Blood Collection

Refer to "6.8 Pharmacokinetics."

8.2 Biomarker Endpoints

- The presence or absence of mutations of the FLT3-ITD gene will be investigated using 2 mL of bone marrow liquid or 4 mL of peripheral blood collected after obtainment of informed consent, but before registration.
- The plasma inhibitory activity of quizartinib on phosphorylated FLT3 and c-Kit proteins will be measured using 2 mL of peripheral blood.

8.3 Anonymization, Storage, and Disposal of Specimens for Biomarker Testing

8.3.1 Anonymization of Specimens

Prior to submission, the specimens will be anonymized with the subject identification code so that patient's personal information cannot be identified. Since the linking table between the subject identification code and their personal information will be strictly retained at the study center, not the sponsor, specimen collection agency, or biomarker assay facility can identify the patient's personal information. The sponsor can interlink biomarker study results to the subject identification code and the study data of the concerned patient.

8.3.2 Storage of Specimens

Considering the possibility that the relationship between the efficacy or safety of the study drug and biomarkers may be additionally measured, and the possibility that the items given in "6.9 FLT3-ITD Mutation Test" and "6.10 Biomarker Study" may be remeasured based on newly obtained knowledge, the submitted specimens will be stored at the biomarker assay facility for a maximum of 5 years after the end of the study. Biomarkers that may be additionally measured are point mutations and deletions in the tyrosine kinase domain of FLT3.

8.3.3 Disposal of Specimens

At the time of expiration of the specimen storage period, the biomarker assay facility will dispose of all the specimens as instructed by the sponsor.
If a patient withdraws consent for the study during the specimen storage period, the

specimens will be disposed of, depending on the location of the specimens at the time, according to the following procedure. If biomarker analysis has been performed at the biomarker assay facility before a patient's withdrawal of consent, the data will not be disposed of.

1) In cases where the specimens are temporarily stored at the study center:
   The investigators will identify the specimens of the patient and dispose of them.
2) In case the specimens are stored at the specimen collection agency or the assay facility:

The investigators will report the subject identification code of the pertinent patient to the sponsor. The sponsor will instruct the specimen collection agency or the assay facility to dispose of the specimens of the patient.

9. SAFETY EVALUATION AND REPORTING

Safety endpoints are defined as AEs, laboratory data, body weight, ECOG PS, vital signs, 12-lead ECG, MUGA/echocardiography, and X-ray examination.

9.1 Adverse Event Collection and Reporting

All clinical AEs (for the definition, see "9.3.1 Definition of Adverse Events") that occur during the period from the day of the first dose of the study drug to the day of post-treatment observation will be recorded on the AE page of the CRF. SAEs that occur during the period from the day of informed consent to before the first dose of the study drug will also be recorded in the CRF.

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 complications/medical history.

AEs and SAEs are to be reported according to the procedures in "9.4 Serious Adverse Events Reporting Procedure for Investigators."

All clinical laboratory results, vital signs, and 12-lead ECG results and findings should be appraised by the investigators to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigators' clinical judgment.

At each visit, the investigators will determine whether any AEs have occurred by evaluating the patient. AEs may be directly observed, reported spontaneously by the

patient or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigators must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in "9.3 Adverse Events." The investigator's assessment must be clearly documented in the site's source documentation.

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.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for preexisting conditions that do not worsen in severity should not be reported as SAEs (refer to Section "9.3.2 Serious Adverse Events" for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigators assesses as related to study drug should also be reported and managed as an SAE.

If any AE has occurred, the investigators will take appropriate actions, notify the sponsor as required, and continue follow-up until the patient recovers to the pre-event condition with resolution or relief of the AE as far as possible (even after the end of the specified observation period). However, even if the AE is not confirmed to have resolved or relieved, if it is judged that the patient's condition remains stable and the safety can be assured, the investigators will explain the matter to the patient, and the follow-up of the study will be completed (treatment of the relevant symptom will be continued).

9.2 Safety Endpoints

Safety endpoints are defined as AEs, laboratory data, body weight, ECOG PS, vital signs, 12-lead ECG, MUGA/echocardiography, and X-ray examination.

9.2.1 Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST ≥ 3 × upper limit of normal [ULN] with simultaneous total bilirubin ≥ 2 × ULN) should always be reported to the sponsor using a Serious Adverse Event Report (SAVER) form, with the investigators' assessment of seriousness, causality, and a detailed narrative.[16)] These events should be reported within 24 hours of investigators' awareness of the event.

If the patient discontinues study drug due to liver enzyme abnormalities, the patient will have additional clinical and laboratory evaluations as described in "5.7 Subject Withdrawal/Discontinuation" in order to determine the nature and severity of the potential liver injury.

9.3 Adverse Events

9.3.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient 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 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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.

The progression of the underlying disease (AML) will be handled as described below:

- Tumor progression will not be handled as an AE. However, tumor progression leading to the outcome of death during the AE collection period should be handled as an SAE (with the name and outcome of the event recorded as "disease progression" and "fatal," respectively).
- Tumor progression resulting in exacerbated signs or symptoms will be handled as an AE.

9.3.2 Serious Adverse Events

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

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization for treatment,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly or birth defect, or
- is an important medical event.

The term “life-threatening” in the definition of “serious” refers to an event in which the patient 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 (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for preexisting conditions that do not worsen in severity are not SAEs.

9.3.3 Severity Assessment

Severity of AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Japanese version. The severity of AEs not included in the CTCAE v4.0 Japanese version will be assessed according to the grades specified in Table 9.3-1.

Table 9.3-1 Evaluation of Severity of Adverse Events

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Severity vs seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event.

9.3.4 Causality Assessment

The investigators should assess causal relationship between an AE and the study drug on the basis of 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 patient's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
    or
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Not related:
  - The AE does not follow a reasonable temporal sequence from study drug administration, or can be reasonably explained by the patient's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.3.5 Action Taken Regarding the Study Drug

- Dose not changed: No change in study drug dosage was made.
- Drug withdrawn: The study drug was permanently stopped.

- Dose reduced: The dosage of the study drug was reduced.
- Drug interrupted: The study drug was temporarily stopped.
- Dose increased: The dosage of the study drug was increased.
- Not applicable: patient died, treatment with the study drug had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.3.6 Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter (OTC) medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.3.7 Adverse Event Outcome

- Recovered/Resolved
  - The patient fully recovered from the AE with no residual effect observed.
- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Not recovered/Not resolved
  - The AE itself is still present and observable.
- Recovered/Resolved with sequelae/residual effect(s) present
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

9.4 Serious Adverse Events Reporting–Procedure for Investigators

All AEs and SAEs will be reported in the CRF.

The following types of events should be reported by the investigator to the sponsor by telephone or on a SAVER form within 24 hours of awareness. The SAVER form for

reporting events to the sponsor should be sent via e-mail or fax.

- SAEs (refer to Section "9.3.2 Serious Adverse Events" for definition)
- Hepatic events meeting combination abnormalities (ALT or AST ≥ 3 × ULN with simultaneous total bilirubin ≥ 2 × ULN) (potential Hy's Law case), both serious and nonserious.

The investigator should report the details of each SAE in writing to the sponsor and the head of the study center. A written report to the head of the study center will be made in accordance with the procedures and format specified by the study center.

All events (serious and nonserious) must be reported with investigators' assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be reported to the sponsor. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative when available. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study center and should not be submitted to the sponsor for SAE reporting purposes.
Urgent safety queries must be followed up and addressed promptly. 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.
The investigator must sign all completed SAVER forms, and then send them as attached documents to the appropriate e-mail address or fax them to the appropriate fax number. For the detailed reporting procedure, refer to the separately prepared procedural document.
The contact information for reporting SAEs is provided in "18.3 Sponsor's Safety Contacts" and the separately prepared procedural document. If there are any questions about reporting SAEs, the clinical monitor etc. should be contacted.

9.5 Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

If a serious adverse drug reaction occurs in other study centers enrolled in this study or other ongoing clinical studies of quizartinib, the sponsor should report to the

investigators, the institutional review board/ethics committee (IRB/EC), and the regulatory authorities.

9.6 Exposure In Utero during Clinical Studies

If it becomes known that a patient or a patient's partner has become pregnant during treatment with the study drug or within 6 months after discontinuation of treatment with the study drug, the investigators must notify the sponsor.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigators to report any pregnancy in a female patient or a male patient's female partner using the form provided by the sponsor (Exposure in Utero Reporting Form). Please contact your study monitor to receive the Exposure in Utero Reporting Form upon learning of a pregnancy. The investigators should make every effort to follow the patient until completion of the pregnancy and complete the Exposure in Utero Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigators should follow the procedures for reporting SAEs outlined in Section 9.4.

9.7 Clinical Laboratory Evaluations

The following items will be measured. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used.

Information will be entered in the CRF on whether measured, date of measurement, and measurement results for the following items.

1) Hematology test
   Red blood cell count, MCV, MCH, MCHC, hemoglobin, hematocrit, white blood cell count, white blood cell differential count (neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelet count, and PT-INR
2) Blood chemistry test
   Total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, ALP, γ-GT, LDH, lipase, BUN, serum creatinine, creatine kinase, uric acid, glucose, electrolytes (K, Na, Cl, Ca, P, Mg), CRP, total cholesterol, LDL, HDL, and triglyceride
3) Urinalysis

Specific gravity, pH, occult blood, glucose, protein, bilirubin, and ketone bodies

9.8 ECOG PS

The date of measurement and the results of investigators' assessment will be recorded in the CRF.

9.9 Vital Signs

Blood pressure and pulse rate will be measured after the patient has rested in a recumbent position for 5 minutes or more.
Information will be entered in the CRF on whether or not measured, date of measurement, and measurement results for the following items.
Systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, height, and body weight

9.10 Electrocardiograms

9.10.1 Measurement Method

ECG will be performed consecutively three times (triplicate ECGs) at intervals of 3 to 5 minutes after patients have remained at rest in the supine position for 10 minutes. The QTcF interval will be determined as the average of three measurements and used for safety evaluation and for making a decision on quizartinib dose increase on Day 16 of Cycle 1 and on Day 1 of Cycle 2 or later. The ECG results will be transferred to the Central ECG Reading Center (eResearch Technology, Inc. [ERT]). The investigators may check the ECGs without waiting for a central assessment if an urgent decision is required to assure the patient's safety at the study center.
If a foreseeable abnormal ECG finding is observed (eg, QTcF > 480 ms), the study center should contact the Central ECG Reading Center to request immediate assessment (within 24 hours), and determine the action to be taken for the patient (dose increase or reduction of the study drug etc.) based on the central assessment results. In this case, triplicate ECGs should be obtained again within 2 hours after the ECG measurement in which the above abnormal finding has been detected, and the results should be submitted to the Central ECG Reading Center.
The analysis results of the Central ECG Reading Center will be regarded as the final ECG data. All QT-related events will be decided using QTcF.
Additional ECG may be performed if the investigators consider it necessary. In such a case, the time of the ECG should be recorded. Triplicate ECGs should be obtained at all

the measurement time points, and the QTcF determined as the average of the three recordings will be used as the representative ECG data.
Whether to measure the ECG or not, date and time of measurement, and investigators' assessment results will be recorded in the CRF.

9.10.2 Measures Taken in Case of QTcF Prolongation

To reduce the risk of arrhythmia caused by quizartinib, laboratory monitoring should be performed to keep blood electrolytes (K^+, Ca^{++}, and Mg^{++}) within the institutional reference ranges, and further to ensure K^+ levels of 4.0 mEq/L or more as far as possible. If Grade 2 or more severe QTcF prolongation occurs, treatment should be given according to the following procedure. In patients for whom treatment with quizartinib is interrupted or the dose of quizartinib is reduced in association with Grade 2 or more severe QTcF prolongation, 12-lead ECG should be performed at any subsequent appropriate timing to carefully confirm whether QTcF prolongation has recovered or not.

Grade 2 (QTcF: 481 ms to 500 ms)

- Measure electrolyte levels (K^+, Ca^{++}, and Mg^{++}) and supply the electrolytes to ensure recovery to the institutional reference ranges.
- Check concomitant drugs, and discontinue drugs that are known to prolong QTcF, as necessary.
- Reduce the dose of quizartinib by one level. It is not necessary to interrupt treatment.
- The dose may be increased to the dose before dose reduction if QTcF prolongation recovers to Grade 1 or less severe after treatment at the reduced dose for at least 28 days. However, whether prolongation of QT interval occurs or not should be confirmed carefully for the first cycle (28 days) after the dose increase.

Grade 3 (QTcF $\geq$ 501 ms)

- Measure electrolyte levels (K^+, Ca^{++}, and Mg^{++}) and supply the electrolytes to ensure recovery to the institutional reference ranges.
- Check concomitant drugs, and discontinue drugs that are known to prolong the QT interval, as necessary.
- Interrupt treatment with quizartinib for a maximum of 14 days. Resume treatment with quizartinib at a one-level reduced dose, relative to the dose immediately before the interruption, if the increase in QTcF interval from baseline is 30 ms or shorter or

the QTcF interval recovers to 450 ms or shorter within 14 days after the onset. If Grade 3 QTcF prolongation occurs, subsequent dose increase is not allowed.

Grade 4 (increased QTcF to 501 ms or longer or a 60 ms or longer change in QTcF from baseline associated with any signs or symptoms of TdP, polymorphic ventricular tachycardia, or any other serious arrhythmia)

- Measure electrolyte levels (K^+, Ca^{++}, and Mg^{++}) and supply the electrolytes to ensure recovery to the institutional reference ranges.
- Check concomitant drugs, and discontinue drugs that are known to prolong the QT interval, as necessary.
- Discontinue treatment with quizartinib.

9.10.3 Chest X-ray Examination

The date of measurement and the results of investigators' assessment will be recorded in the CRF.

9.10.4 MUGA Scan or Echocardiography

The date of measurement and LVEF (%) will be recorded in the CRF.

10. OTHER ASSESSMENTS

Not applicable

11. STATISTICAL METHODS

11.1 General Statistical Considerations

The primary objective (hypothesis) of this study is to confirm that the CRc rate with quizartinib monotherapy is at least 23.5% in Japanese patients with FLT3-ITD positive relapsed or refractory AML.

Efficacy analyses will be performed using the efficacy analysis set. Safety, pharmacokinetic, and biomarker analyses will be performed using the safety analysis set, the pharmacokinetic analysis set, and the biomarker analysis set, respectively.

The analyses, excluding pharmacokinetic and biomarker analyses, in this study will be performed in all patients included in each analysis set regarded as one dose group, whether the dose is increased or reduced.

Unless otherwise noted, continuous variables will be summarized by the number of patients analyzed, arithmetic mean, standard deviation, minimum, median, and maximum,

whereas categorical variables will be summarized by frequency and proportion.
Baseline values of each patient, unless otherwise specified, will be the last observed values that are available before the first dose of the study drug. Analyses of changes from baseline (eg, absolute change, shift table) will be performed on patients with baseline values and at least one post-treatment value available.
This study will be conducted using a two-stage design, and interim analysis is planned to be performed once. The details of interim analysis are shown in Section 11.4.

11.2 Analysis Sets

The sponsor will finalize the population flag of individual patients for each analysis set after CRF lock. Patients with major Good Clinical Practice (GCP) violations (eg, a violation of the informed consent procedure, a major violation of study procedures) will be excluded from all analysis sets.

- All enrolled patients will include all patients who have signed the ICF.
- All registered patients will include all patients who have signed the ICF and are assessed as eligible for the study.
- The safety analysis set will include all patients who have signed the ICF and received at least one dose of the study drug.
- The efficacy analysis set will include patients who have signed the ICF (including consent for measurement of FLT3-ITD mutations), have a positive result of the FLT3-ITD mutation test performed at Navigate BioPharma, and have received at least one dose of the study drug.
- The pharmacokinetic analysis set will include patients who have signed the ICF and received at least one dose of the study drug, and whose plasma drug concentration data obtained are available for at least one time point after the start of treatment with the study drug.
- The biomarker analysis set will include patients who have signed the ICF and received at least one dose of the study drug, and whose biomarker data shown in Section 6.10 are available for at least one time point after the start of treatment with the study drug.

11.3 Statistical Analyses

11.3.1 Efficacy Analyses

Efficacy analyses will be performed in the efficacy analysis set.

11.3.1.1 Primary Efficacy Analyses

For the CRc rate, frequency tables will be prepared, and the 90% and 95% confidence intervals (CIs) will be calculated.

11.3.1.2 Secondary Efficacy Analyses

For the best response and the response rate, frequency tables will be prepared, and the 95% CI will be calculated.

For OS, event-free survival, and leukemia-free survival, Kaplan-Meier curves will be prepared, and medial survival and the 95% CI will be calculated using the method of Brookmeyer and Crowley.

For the transplantation rate, frequency tables will be prepared, and the 95% CI will be calculated.

11.3.1.3 Exploratory Efficacy Analyses

Not applicable

11.3.2 Pharmacokinetic/Pharmacodynamic Analyses

11.3.2.1 Pharmacokinetic Analyses

In the pharmacokinetic analysis set, summary statistics of the plasma concentrations of quizartinib and AC886 will be calculated by dose at each time point, and plasma concentration-time profiles will be prepared. Summary statistics of pharmacokinetic parameters will be calculated by dose at each time point.

A population pharmacokinetic analysis of quizartinib and quizartinib exposure-response analysis will be performed to evaluate the relationship between the dose and exposure as well as between exposure and the efficacy or safety endpoints. If population pharmacokinetic and exposure-response analyses are performed, the reports should be prepared separately.

11.3.2.2 Pharmacodynamic Analyses

Not applicable

11.3.2.3 Biomarker Analyses

In the biomarker analysis set, measured values of plasma inhibitory activity of quizartinib on phosphorylated FLT3 and c-Kit proteins will be summarized at each time point.

11.3.2.4 Pharmacogenomic Analyses

Not applicable

11.3.3 Safety Analyses

Safety analyses will be performed in the safety analysis set.
AEs that occur or worsen relative to the pre-treatment state after the first dose of the study drug (treatment emergent AEs [TEAEs]) will be tabulated. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology developed by the ICH, and be tabulated by body organ group using the MedDRA system organ class (SOC) and by AE term using preferred terms (PTs).

11.3.3.1 Adverse Event Analyses

For TEAEs and TEAEs assessed as "related" to the study drug, frequency tables will be prepared as classified below. The grade of each AE will be assessed according to the CTCAE v4.0 Japanese version. In the tabulation by grade, only the highest-grade event in each patient will be included.

- TEAEs (by grade; including classification into Grade 3 or more severe events)
- Serious TEAEs
- Patients who have interrupted treatment with the study drug due to TEAEs
- Patients with treatment discontinuation because of TEAE

For TEAEs and TEAEs assessed as "related" to the study drug, frequency tables will be prepared by event as classified below. The grade of each AE will be assessed according to the CTCAE v4.0 Japanese version. If a patient reports the same event several times, only the highest-grade event will be counted for tabulation.

- TEAEs
- TEAEs by grade (including classification into Grade 2 or less severe events and Grade 3 or more severe events)
- Serious TEAEs
- TEAEs leading to interruption of treatment with the study drug
- TEAEs causing treatment discontinuation

11.3.3.2 Clinical Laboratory Evaluation Analyses

For hematology and blood chemistry tests, summary statistics of measured values and changes from baseline will be calculated at each time point. For urinalysis (except

specific gravity), shift tables of measured values at baseline and those at each time point will be prepared. For specific gravity, summary statistics will be calculated at each time point.
The number and proportion of patients who meet the criteria specified in the Food and Drug Administration (FDA) Guidance for Industry Drug-induced Liver Injury (DILI)[16)] in terms of ALT, AST, total bilirubin, and ALP will be calculated, and evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be prepared.

11.3.3.3 Vital Sign Analyses

For blood pressure (systolic and diastolic), pulse rate, body temperature, and body weight, summary statistics of measured values and changes from baseline will be calculated at each time point.

11.3.3.4 Electrocardiogram Analyses

For 12-lead ECG findings, shift tables of normal-abnormal assessments at baseline and each time point will be prepared. For PR, QRS, RR, QT, QTcB, and QTcF intervals and heart rate, summary statistics of measured values and changes from baseline will be calculated at each time point. For QTcF, frequency tables will also be prepared according to the following categories.
Absolute QTcF:

- QTcF > 450 ms
- QTcF > 480 ms
- QTcF > 500 ms

Changes in QTcF from baseline:

- Increase in QTcF from baseline > 30 ms
- Increase in QTcF from baseline > 60 ms

11.3.3.5 Analyses of Physical Findings

Not applicable

11.3.3.6 Exploratory Safety Analyses

Not applicable

11.3.4 Other Analyses

Not applicable

11.3.5 Blinded Review

Not applicable

11.4 Interim Analysis

This study is planned with a two-stage design; in Stage 1, interim analysis will be performed when 25 patients are included in the efficacy analysis set. If it is decided to continue the study based on the interim analysis (for the assessment criteria, see "11.4.3 Criteria"), registration of patients will be continued until 41 patients are included in the efficacy analysis set (16 patients in Stage 2). Registration of patients will be continued during the course of the interim analysis.

11.4.1 Purposes of the Interim Analysis

In this study, interim analysis that includes early termination of the study due to efficacy and futility is planned for the following reasons. In the interim analysis, the secondary efficacy endpoints, safety, pharmacokinetics, and biomarkers will be evaluated in addition to the primary endpoint, CRc rate.

Since the sample size of this study is calculated based on the alternative hypothesis that the CRc rate is 42%, which is the lower limit of the CRc rate of 42% to 47% obtained in overseas Phase 2 studies of AC220 monotherapy in patients with FLT3-ITD positive relapsed or refractory AML (Studies AC220-002 and 2689-CL-2004) (see Section 11.5), the true CRc rate with quizartinib in this study may be higher than 42%. In such a case, to allow early completion of this study, interim analysis including early termination due to efficacy is planned. In addition, since the results of overall Phase 2 studies are highly uncertain due to a limited number of patients, taking the possibility that the true CRc rate with quizartinib may be about 23.5%, which is set as the threshold level into consideration, early termination due to futility is also included in the requirements for interim analysis.

11.4.2 Possible Options to Be Taken at Interim Analysis

The following decisions will be made at the interim analysis. If it is decided to terminate the study early, the registration of patients will be discontinued; however, treatment with the study drug in patients who continue receiving the study drug will be continued until "5.7.1 Discontinuation Criteria for Treatment with the Study Drug" are met.

- Continuation of the study
- Early termination of the study due to efficacy
- Early termination of the study due to futility

11.4.3 Criteria

The assessment criteria in Stage 1 (25 patients will be chosen from the efficacy analysis set in the order of registration) and at the end of Stage 2 (41 patients will be chosen from the efficacy analysis set in the order of registration) are shown below. Concerning patients for whom the study is continued as of the data cut-off date (see below) of the interim analysis, the best response will be calculated from the data collected up to the data cut-off date, and whether CRc is achieved or not will be assessed.

<Stage 1>

- The study will be continued if CRc is achieved in 4 to 10 patients.
- The study will be early terminated due to efficacy if CRc is achieved in 11 or more patients.
- The study will be early terminated due to futility if CRc is achieved in 3 or fewer patients.

<Stage 2>

- Treatment will be determined to be effective (rejection of the null hypothesis) if CRc is achieved in 15 or more patients.

Data cut-off date:

The day when the best response is assessed as CR, CRp, or CRi, the day when treatment with the study drug is discontinued, or Day 1 of Cycle 4, whichever comes first, will be calculated for each patient. The latest day in the 25 patients included in the interim analysis is regarded as the data cut-off date. The above procedure will also apply to analysis at the end of Stage 2.

11.4.4 Data Monitoring Committee

An in-house Data Monitoring Committee, which consists of medical monitors, persons in charge of clinical procedures, biostatisticians, persons in charge of pharmacokinetic analysis, and persons in charge of modeling & simulation, will be established and will have responsibility to review the interim analysis results. In principle, the Data Monitoring Committee is supposed to make a decision on early termination of the study in accordance with "11.4.3 Criteria." However, continuation of the study may be

decided depending on the results of safety assessment of the interim analysis. In the review process, the Data Monitoring Committee might consult with external hematology oncology specialists as necessary. The review content and final decision on interim analysis will be recorded in the meeting minutes.

11.5 Determination of Sample Size

The remission induction rate is remarkably low in patients with relapsed or refractory AML, compared with anticancer therapy introduced in patients with newly diagnosed AML, and it is as low as 12.8% (76/596) according to the report by Giles et al.[15] The results of FLT3-ITD-positive AML patients have also been reported by Ravandi[17] and Levis[18] as follows: The rate of remission induction with salvage therapy was 23.5% (8/34) in patients with first relapsed AML, and the rate of remission induction was 11.3% (6/53) in the subgroup of patients who had a poor prognosis defined as initial remission sustained for 6 months or shorter after the initial treatment. In this way, considering that the remission induction rate in patients with relapsed or refractory AML varies among the reports and that the data of CRi, which is one of the elements comprising CRc, are not available in some reports, the threshold of the CRc rate in this study was set at 23.5% as the most conservative value among the values that are available for reference.
Meanwhile, in preceding overseas Phase 2 studies of quizartinib monotherapy in patients with FLT3-ITD-positive relapsed or refractory AML (Studies AC220-002 and 2689-CL-2004), the CRc rate has been reported to be 42% to 47% at several doses of quizartinib including 30 mg and 60 mg. The expected CRc rate with quizartinib in this study was therefore assumed to be 42%.
The design shown in Table 11.5-1 was established to satisfy the following conditions, with a one-sided 5% significance level and 80% power, in reference to the optimal two-stage design under the alternative hypothesis proposed by Mander and Thompson.[19]

- The number of patients evaluated in Stage 1 is approximately 25 (to assure a certain amount of safety information even if the study is early terminated in Stage 1).
- If the study is early terminated due to futility, the observed CRc rate is 12% or less (less than the lower limit of the remission induction rate reported).
- The probability of early termination due to efficacy under the condition of the expected CRc rate (42%) is approximately 50%.

Table 11.5-1 Number of Patients Evaluated at Each Stage and Assessment Criteria

	This Study	Mander*[1]
No. of patients assessed in Stage 1	25	19
Criteria for discontinuation due to futility in Stage 1	≤ 3	≤ 4
Criteria for discontinuation due to efficacy in Stage 1	≥ 11	≥ 9
No. of patients assessed at the end of Stage 2	41	41
Assessment criteria for efficacy at the end of Stage 2	≥ 15	≥ 15
Expected No. of patients under the alternative hypothesis	33.0	31.1

*1 Optimal two stage design under the alternative hypothesis proposed by Mander and Thompson

Based on the above, registration of patients will be continued until 25 patients assessable for efficacy are enrolled in Stage 1 and 16 patients assessable for efficacy are enrolled in Stage 2.
Shown below are the operating characteristics when the two-stage design applies to this study.

CRc Rate (True Value)	Probability of Discontinuation Due to Futility (Stage 1)	Probability of Discontinuation Due to Efficacy (Stage 1)	Probability of Assessment as Futility (Entire Study)	Probability of Assessment as Efficacy (Entire Study)
23.5%	0.128	0.019	0.952	0.048
42.0%	0.001	0.496	0.186	0.814

11.6 Statistical Analysis Process

In this study, statistical analyses will be performed by a contract research organization (CRO) using SAS® Version 9.2 or a later version (SAS Institute Inc.) and WinNonliln (Version 6.0 or a later version). The detailed methods of statistical analyses will be specified in the separately prepared statistical analysis plan (SAP). To maintain the integrity of conclusions drawn from the statistical analyses and the study, the SAP should be fixed before database lock. If modifications to the SAP lead to a change in major contents of the protocol, the protocol will be amended. In the event of any deviation from the protocol-specified statistical analyses, the details will be described in the SAP.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The head of the study center and the investigator will provide direct access to all study-related documents, including source documents, at the implementation of monitoring and auditing by the sponsor as well as inspections by the regulatory authorities and the IRB. The sponsor will have direct access to all study-related documents, including source documents, at the study center when performing monitoring

and auditing to ensure appropriate implementation of the study and the reliability of the data. The sponsor will confer with the investigator in advance regarding the procedures for source document verification.

12.1 Monitoring and Inspections

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

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study center. The monitor is responsible for inspecting the CRFs 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 CRFs. 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 center facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings.

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

12.2 Data Collection

12.2.1 Completion of the Case Report Forms

The investigator, subinvestigator, or study staff will enter the data in the CRF in accordance with the CRF Completion Guideline that are provided by the sponsor.

CRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The CRF will be completed, reviewed, and signed off or e-signed by the investigator.
If the study employs paper CRFs, the investigator will sign and date the indicated places on the CRF. These signatures will indicate that the investigator inspected or reviewed the data on the CRF and the data queries, and agrees with the content.
If the study employs electronic data capturing (EDC), the investigator e-signs according to the study data flow.
Any clinical data entered in the CRF will be subjected to these data management procedures and will be included in the final study datasets according to Clinical Data Interchange Standards Consortium (CDISC) standards.

Daiichi Sankyo or MPI will supply electric case report forms (eCRFs). Daiichi Sankyo or MPI must complete eCRFs for each of subjects who have signed the ICF for the FLT3-ITD test as well as subjects who have signed the ICF for participation in the study and have undergone the screening test. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's audit trail.

12.2.2 Precautions for Entering Data in the Case Report Form

In the study, the CRF will be prepared by the investigator, and the measurement reports of 12-lead ECG, pharmacokinetics, and biomarkers will be prepared by each central laboratory. In this study, an electronic CRF will be entered using the EDC system (Table 12.2-1), which is designed to prepare electronic CRFs. The CRF (including an audit trail) will be prepared for each subject and the one that was signed by the investigator will be handled as the original. A validated EDC system will be used in the study.

Table 12.2-1 EDC System

EDC system name	[redacted]
EDC system development corporation	Medidata Solutions, Inc.
How to enter data	Data entry via the web interface
Terminal for data entry	PC at the study center
OS prohibited	None
Browser	[redacted] supports any browser that conforms to HTML 5, and CSS2. JavaScript needs to be enabled in the browser.
Recommended screen resolution	1024 × 764 resolution or higher
Recommended connection speed	128 kbps or higher
Others	Adobe Flash Player: ver. 10 or higher

A CRF will be prepared for subjects who have provided informed consent for participation in the study and for the FLT3-ITD mutation test performed before the start of the study although they have not received the study drug due to a negative-result of the FLT3-ITD mutation test.

12.3 Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the sponsor.

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data according to specifications given to the sponsor. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. 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 in accordance with the data management plan.

SAEs in the clinical database will be reconciled to the safety database.

All AEs and complications/medical history will be coded using MedDRA. Prior and concomitant medications will be coded using the World Health Organization Drug Reference (WHODRUG).

12.4 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 make entries and/or corrections on CRFs will be included on the Signature List.

The investigator will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date and outcome of screening process.
The investigator will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.
The investigator 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 CRF data are obtained. These include but are not limited to hospital records, medical record, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of the study drug, regulatory documents (eg, protocol and amendments, IRB/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 center (Trial Master File). Source documents include all recordings, observations, and notations of clinical activities and all 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 the institution or study center policy. Prior to transfer or destruction of these records, the sponsor must be notified in writing and be given the opportunity to further store such records.

12.5 Record Keeping

The head of the study center or the person responsible for record keeping are responsible for maintaining a comprehensive and centralized filing system (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 CRFs (copy), ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study,

and all correspondence to and from the IRB/EC and the sponsor.

- Study drug-related records containing record of confirmation of receipt by the study center, Drug Accountability Record, study drug return form, study drug storage/management record (copy), and other correspondence

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

All study related essential documentation will be retained by the head of the study center or the person responsible for record keeping until at least 3 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 3 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 regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/study center as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, study center, 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 of the new responsible person and/or the new location.

13. Payment and Insurance

13.1 Payment

Prior to the start of the study, the investigator or the study center will conclude a study contract with the sponsor and/or the CRO. This contract contains the information on payment agreed upon by the concerned parties.

13.2 Payment, Compensation for Study-related Injury, and Insurance

The sponsor will purchase an insurance policy so that subjects who may suffer any study-related injury can receive compensation.
Payment, compensation for study-related injury, and insurance are covered by a separate contract on the conditions agreed upon by the parties.

14. PUBLICATION POLICY

No information obtained from the study may be published partially or entirely without prior consultation with the sponsor. The methods of publication will be determined by the sponsor. Utmost caution should be exercised to protect the privacy of subjects when information is published. The sponsor will use information obtained from the study for the purpose of application for manufacturing/marketing approval of the investigational drug. If the investigational drug is approved, information about the study may be partially disclosed in accordance with the "Act on Access to Information Held by Administrative Organs (Act No. 42, dated 14 May 1999)," "Act on Access to Information Held by Independent Administrative Agencies (Act No. 140, dated 05 Dec 2001)," and "Notification concerning publication of information on new drug approvals (PFSB/ELD Notification No. 0422001, dated 22 Apr 2005)." Utmost caution should be exercised to protect the privacy of subjects when disclosing information.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1 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 GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- "Ordinance on Good Clinical Practice" (MHW Ordinance No. 28, dated 27 Mar 1997)
- Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (effective as of 25 Nov 2014)

Human genome/gene analysis and banking of clinical specimens for genome/gene analysis, and research using the specimens, which are planned in the study, will be performed in adherence to the "Ethical Guidelines for Human Genome/Gene Analysis Research" and "Ethical Guidelines for Clinical Studies," in addition to the above regulations (only at the study centers that are granted approval for the conduct of genome/gene analysis or banking of clinical specimens for genomic/genetic analysis).

15.2 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 CRFs or other documents submitted to the sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not for submission to the sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the investigator.

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

15.3 Informed Consent

The investigator should provide subjects with sufficient explanations about the details of the study including the objectives, methods, expected benefits, and foreseeable risks prior to the FLT3-ITD mutation test and/or their participation in the study. It is the investigator's responsibility to obtain subjects' written informed consent of their free will at the protocol-specified timing or before the start of treatment with the study drug. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

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 consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

The subject's signed ICF 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 study center's policy, and a copy of the signed consent form should be provided to the subject. The date and time

(if applicable) that informed consent was given should be recorded on the CRF.
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 the subject's participation and, if possible, signed the ICF. 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.
The sponsor shall provide a draft ICF template for the study and/or FLT3-ITD mutation test so that the investigator can prepare the documents used at his/her own study center. The investigator will be notified in writing by the sponsor if these forms are amended in any way.
Data collection using the EDC system will be implemented in accordance with the "Use of Electromagnetic Records and Electronic Signatures in Applications, etc. for Approval of, or License for Pharmaceuticals, etc." (PFSB Notification No. 0401022).

15.4 Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.
Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.
The investigator and/or the sponsor must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF.
The investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study center and other AE reports received from the sponsor/CRO, in accordance with local procedures.
In accordance with the regulatory requirements of the home country, the sponsor's regulatory affairs group or designee should confirm that all legal aspects have been covered and that approval of the applicable regulatory authorities has been obtained prior to the start of the study, and ensure that changes to the original protocol and other related

study documents are made only after they have been approved by the applicable regulatory authorities.
In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable regulatory authorities in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the sponsor should be informed immediately.
In addition, the investigator will inform the sponsor immediately 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 noncompliance that the investigator becomes aware of.

15.5 Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities, and which was given approval by the IRBs/ECs.
A deviation to any protocol procedure or waiver of 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 of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.
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 dose of the study drug, data should be collected for safety purposes.
If applicable, the investigator should notify the IRB of deviations from the protocol.

15.6 Provision of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the sponsor will inform all investigators involved in the clinical study, IRBs/ECs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.
The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/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.

15.7 Protocol Amendment

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by Daiichi Sankyo or the CRO. Changes made by such amendments will be documented in a "Summary of Changes" document. If the protocol is updated, the sponsor will newly obtain written agreement of the investigator and implement the procedures specified by the study center.
A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8 Discontinuation of the Study

If any of the following occurs and the sponsor judges that continuation of the study is difficult, the sponsor will temporarily discontinue the study partially or entirely. The sponsor will then determine whether to permanently discontinue the study partially or entirely, and document the decision.

1) If any new safety information regarding the study drug, or information regarding SAEs is obtained
2) If any major GCP violation or significant protocol deviation is committed by the sponsor, the study center, or the investigator
3) If any other new information of such relevance is obtained during the study

Upon the decision of partial or entire discontinuation of study in consultation with the medical expert etc., the sponsor will promptly notify the head of the study center in writing of the fact with the reason. The head of the study center will promptly notify the investigator and the IRB in writing of the fact with the reason.
If the study is discontinued permanently or temporarily for any reason, the investigator will promptly notify the subjects participating in the study of the fact, and take appropriate actions and perform the necessary tests to verify the safety of subjects.

16. Others

16.1 Payment for Participation, Compensation for Study-related Injuries, and Insurance

16.1.1 Payment for Participation

As payments for reducing the subject's burden, the study center will pay subjects from the funds paid by the sponsor to the study center according to the separately specified regulations of the study center.

16.1.2 Compensation for Study-related Injuries

If a subject experiences any study-related injury resulting from participation in the study, the investigator or subinvestigator will take the necessary actions, including treatment. If the subject makes a claim for study-related injury, the sponsor will be promptly notified. The sponsor will specify the procedures for compensation for study-related injury resulting from participation in the study and take actions such as purchase of an insurance policy. The sponsor will bear the expenses that are paid by the subject for treatment of the injury, excluding the amount covered by health insurance, etc. The sponsor shall also pay medical allowance for study-related injuries requiring hospitalization for treatment, based on the amount specified under the Relief System for Sufferers from Adverse Drug Reactions. However, the sponsor will not agree to indemnify the subject for study-related injuries arising under the following circumstances:

1) If there is clear evidence of any other cause of study-related injury.
2) If there is no reasonable temporal relationship between administration of the study drug and the occurrence of the study-related injury.
3) If a perpetrator has been identified (for instance, traffic accident).
4) If there were no therapeutic benefits because of lack of efficacy.
5) If a subject or a subject's partner is found to be pregnant during the study.
6) If there is any protocol violation without due reason.

If a study-related injury is caused by an intentional act or gross negligence on the part of the study center or the subject, compensation may not be paid or may be reduced.

16.1.3 Insurance

In case of compensation for study-related injury, the sponsor will purchase an insurance policy as required. In case of study-related injury due to medical malpractice, the study

center will purchase an insurance policy and take other measures as required.

16.1.4 Notifying Any Other Physicians Treating Patients of Their Study Participation

If a registered patient has to receive treatment by another physician, the investigator or subinvestigator must inform the physician of the patient's participation in the study with the patient's approval.

The investigator or subinvestigator will ask patients who have provided informed consent whether they are being treated by another physician (eg, a physician in another department of the study center or at another medical institution) or not. If the patient is receiving treatment by another physician, the investigator or subinvestigator will inform the physician of the patient's participation in the study with the patient's approval and record the provision of this information in the medical record, etc.

16.1.5 Quality Control and Quality Assurance

The sponsor will implement the quality assurance and quality control system in accordance with the standard operating procedures specified by the sponsor to ensure that the implementation of the study and the generation, recording, and reporting of data are in compliance with the following:

1) The clinical study protocol
2) Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter, the PMD Act)
3) GCP ordinance

In addition, the sponsor will perform quality control at each stage of data handling to ensure the reliability and proper processing of all study-related data. The methods for quality control will be prepared in advance in accordance with the standard operating procedure specified by the sponsor, and the implementation will be recorded.

The sponsor's responsible auditor will perform GCP auditing as part of quality assurance operations to determine whether the study is conducted in compliance with GCP, the clinical study protocol, and the written procedures independently and separately from the regular monitoring and study quality control operations.

17. Data and Safety Monitoring Board

Not applicable

18. Address List

18.1 Sponsor's Responsible Medical Officer

[redacted]
[redacted]
[redacted], Japan
TEL: [redacted] FAX: [redacted]

18.2 Sponsor's Clinical Study Leader

[redacted]
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
TEL: [redacted] FAX: [redacted]

18.3 Sponsor's Safety Contacts

[redacted]
3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan
TEL: [redacted] FAX: [redacted]

18.4 Medical Monitor

[redacted]
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
TEL: [redacted]

18.5 Contract Research Organization

Mediscience Planning Inc.
[redacted], Japan
TEL [redacted] FAX: [redacted]

18.6 EDC Vendor

Medidata Solutions, Inc.
[redacted]
[redacted], USA
TEL: [redacted] FAX: [redacted]

18.7 IXRS Vendor

Not applicable

18.8 Central Laboratory

18.8.1 Measurement of Drug Concentrations

BASi corporate

[redacted] USA

TEL: [redacted] FAX: [redacted]

18.8.2 Investigation of Mutations of the FLT3-ITD Gene

Navigate BioPharma Services, Inc.

[redacted], USA

TEL: [redacted] FAX: [redacted]

SRL, Inc.

[redacted] Japan

TEL: [redacted] FAX: [redacted]

18.8.3 Agency for Collection etc. of Specimens for Drug Concentration Measurement and Investigation of Mutations of the FLT3-ITD Gene

SRL Medisearch Inc.

[redacted] Japan

TEL: [redacted] FAX: [redacted]

18.8.4 12-lead Electrocardiogram Measurement and Assessment

eResearch Technology, Inc.

[redacted], USA

TEL: [redacted] FAX: [redacted]

18.9 Sponsor's Biostatistician

[redacted]

1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

TEL: [redacted] FAX: [redacted]

18.10 Data Safety Monitoring Board

Not applicable

18.11 Emergency Contact Information

1) Night hours (18:00 to 9:00) and Saturdays, Sundays, and holidays (all day):
   Daiichi Sankyo Emergency Center
   TEL: [redacted]

2) Daytime (9:00 to 18:00) from Monday through Friday (except holidays):
   [redacted]
   Oncology Clinical Development Department, R&D Division, Daiichi Sankyo Co., Ltd.
   TEL: [redacted] FAX: [redacted]

19. REFERENCES

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Oct 2009)

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20. APPENDICES/ATTACHMENTS

Appendix 1 Study Schedule
Appendix 2 ECOG Performance Status (PS)
Appendix 3 New York Heart Association (NYHA) Functional Classification
Appendix 4 List of CYP3A4 Inhibitors

Attachment 1 List of Study Centers
Attachment 2 Study Administrative Structure

Appendix 1 Study Schedule

	Screening (≤ 14 days before Registration)	Cycle 1				Cycle 2		Cycle 3	Cycle 4 and Thereafter	At Withdrawal	Post treatment Observation	Follow up
		Day 1	Day 2 and 8	Day 15	Day 16	Day 1	Day 15	Day 1	Day 1		30 Days after the Last Dose	
Acceptable limit (unit: days)			Day 2: Scheduled Day Day 8: ±1	±1	(Must Be the Day Following Day 15)	±3	±1	±3	±3	3 to +7	+15	Every 3 Months
Informed consent	●											
FLT3 ITD test	●*1											
Administration of quizartinib (at the study center)		●*2	●*2	●*2	●*2	●*2	●*2	●*2	●*2			
Medical history/complications	●											
Vital sign measurement	●	●	●	●		●	●	●	●	●	●	
ECOG PS/body weight	●	●				●		●	●	●	●	
Height	●											
Laboratory tests (hematology, blood chemistry, urinalysis)	●	●*3	●*3	●*3		●*3	●*3	●*3	●*3	●	●	
Pregnancy test	●											
HIV antibody	●*4											
12 lead ECG	●*5	●*5	●*5	●*5		●*5		●*5	●*5	●*5		
X ray examination	●	○ (as needed)										
MUGA scan or echocardiography	●*6	○ (as needed)										
Assessment of bone marrow findings (tumor assessment)	●*7					●*7		●*7	●*7	●*7		
Measurement of drug concentrations		●*8	●*8	●*8	●*8	●*8		●*8				
Inhibitory activity on phosphorylated FLT3 and c Kit proteins		●*9	●*9	●*9		●*9						
AEs	●*10											
Assessment of concomitant drugs and therapies		●										
Investigation of survival status Other leukemia treatment etc.											●	●

1) FLT3 ITD levels will be measured using a bone marrow specimen or peripheral blood. The collected bone marrow specimen or peripheral blood will immediately be submitted to the specimen collection agency.
2) Quizartinib will be administered on Days 1, 2, 8, 15, and 16 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of Cycle 3, and Day 1 of Cycle 4 and subsequent cycles at the study center. Quizartinib may be administered at home on the other days.

3) To be measured before administration of the study drug.
4) To be performed within 120 days before registration.
5) ECG will be measured three times (triplicate ECGs) at each of the following time points. Triplicate ECGs will be obtained at least once weekly for the first 2 weeks after increasing the dose of quizartinib to carefully confirm the QTcF interval.
   Screening, Day 1 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 2 and Day 8 of Cycle 1 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 1 of Cycle 2 ([if the dose of quizartinib is increased on Day 16 of Cycle 1]: before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug, [if the dose of quizartinib is not increased on Day 16 of Cycle 1]: before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 1 of Cycle 3 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), and Cycle 4 thereafter (before administration of the study drug on Day 1 of each cycle)
6) A multiple gated acquisition (MUGA) scan or echocardiography must be performed at screening except in case LVEF is 45% or more within 1 month before registration.
7) It is desirable to assess bone marrow findings with specimens obtained by both bone marrow aspiration and biopsy; however, bone marrow biopsy may be skipped if the antitumor effect can be evaluated adequately only by bone marrow aspiration in the opinion of the investigators. Assessment of bone marrow findings will be performed at screening (it is desirable to obtain the specimen within 14 days before registration; however, the specimen collected before the time may be used with the consent of the medical monitor etc.), on Day 1 of Cycle 2 and subsequent cycles, at the time of discontinuation of the study, and other time points if assessment is considered necessary by the investigators. For patients achieving CR, CRp, or CRi, bone marrow findings will be assessed every 3 cycles.
8) A plasma specimen for pharmacokinetic measurement will be collected at the following specified time points. If ECG and blood collection for pharmacokinetics (PK) are scheduled at the same time, blood collection for PK will be performed immediately after the end of ECG.
   Day 1 of Cycle 1 (before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug), Day 8 of Cycle 1 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug), Day 1 of Cycle 2 ([if the dose of quizartinib is increased on Day 16 of Cycle 1]: before administration of the study drug and at 1, 2, 4, 6, and 24 hours after the end of administration of the study drug, [if the dose of quizartinib is not increased on Day 16 of Cycle 1]: before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug), and Day 1 of Cycle 3 (before administration of the study drug and at 2 to 4 hours after the end of administration of the study drug).
9) A specimen for measurement of inhibitory activity on phosphorylated FLT3 and c Kit proteins will be collected at the following specified time points.
   Day 1 of Cycle 1 (before administration of the study drug and at 2, 4, and 6 hours after the end of administration of the study drug), Day 8 of Cycle 1 (before administration of the study drug), Day 15 of Cycle 1 (before administration of the study drug), and Day 1 of Cycle 2 (before administration of the study drug).
10) Only information on SAEs will be collected during the period from the day of informed consent to before the first dose of the study drug.

Appendix 2

ECOG Performance Status (PS)

Score	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 3

New York Heart Association (NYHA) Functional Classification

Class	Symptoms
Class 0	Patients without cardiac disease and with no limitation of physical activity.
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 4

List of CYP3A4 Inhibitors

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
Itraconazole	Atazanavir	Atorvastatin
Indinavir	Aprepitant	Amiodarone
Clarithromycin	Amprenavir	Amlodipine
Grapefruit	Istradefylline	Alprazolam
Grapefruit juice	Imatinib	Ginkgo extract
Cobicistat	Erythromycin	Isoniazid
Saquinavir	Crizotinib	Chlorzoxazone
Telaprevir	Ciclosporin	Oral contraceptives
Voriconazole	Ciprofloxacin	Goldenseal
Nelfinavir	Diltiazem	Ciclosporin
Ritonavir	Darunavir	Cimetidine
Lopinavir	Fluconazole	Cilostazol
	Verapamil	Tacrolimus
	Fosamprenavir	Nilotinib
	Miconazole	Pazopanib
	Tofisopam	Bicalutamide
		Fluvoxamine
		Fosaprepitant
		Ranitidine
		Lapatinib

Drugs in the table are categorized based on the drug-drug interaction database (http://www.druginteractioninfo.org/) and its base data, clinical drug-drug interaction studies with indicator drugs reported in the academic literature, as well as by checking package inserts of the concerned drugs, and then listing them. Drugs for topical use and prescription combination agents are not listed in the table.