Protocol No.: AC220-A-J102

Clinical Study Protocol

A Phase 1b Clinical Study of Quizartinib (AC220) –Evaluation of the Safety and Pharmacokinetics of Quizartinib in Combination with Standard Induction and Consolidation Therapy in Japanese Patients with Initially Diagnosed Acute Myeloid Leukemia–

Sponsor: Daiichi Sankyo Co., Ltd.

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PROTOCOL SYNOPSIS

Protocol number	AC220-A-J102
Investigational substance code	AC220
Generic name (r-INN)	Quizartinib
Study title	A Phase 1b Clinical Study of Quizartinib (AC220) –Evaluation of the Safety and Pharmacokinetics of Quizartinib in Combination with Standard Induction and Consolidation Therapy in Japanese Patients with Initially Diagnosed Acute Myeloid Leukemia–
Phase of development	Phase 1b
Planned indication	Acute myeloid leukemia (AML)
Study objectives	Primary objective: To evaluate the safety and pharmacokinetics of quizartinib in combination with standard induction and consolidation therapy in Japanese patients with initially diagnosed AML, and to determine the dose for subsequent phases of development. Secondary objectives: • Exploratory study of quizartinib-related biomarkers • Exploratory evaluation of antitumor effect Type of study objectives: Safety / pharmacodynamics / pharmacokinetics / tolerability / pharmacogenomics
Study design	Type of study: Interventional Type of intervention: Pharmaceutical drugs Type of proposed indications: Treatment Study design: Single arm Level of blinding: Open-label Type and presence/absence of comparator: Absent Presence/absence of randomization: Absent Subject observation period: From informed consent to the end of the post-treatment observation period Presence/absence of add-on to standard therapy: Present Regimen of standard therapy: Cytarabine and an anthracycline

<table>
<tr><td></td><td>drug</td></tr>
<tr><td>Planned study period</td><td>1 Jul 2016 to 31 Dec 2017</td></tr>
<tr><td>Study country</td><td>Japan</td></tr>
<tr><td>Study center</td><td>To be determined</td></tr>
<tr><td>Planned sample size</td><td>Six to twelve patients (minimum of 3 patients at each level, a total of 6 patients)</td></tr>
<tr><td>Study population (Inclusion and exclusion criteria)</td><td><Inclusion criteria>
1) Provision of written informed consent for participation in the study.
2) Age ≥ 20 years and ≤ 75 years at the time of registration in the study
3) AML patients (including those with a history of myelodysplastic syndrome [MDS]) who have not previously received other treatments (including quizartinib) than those listed below
• Leukapheresis
• Treatment with hydroxycarbamide for control of the white blood cell count
• Cranial radiation for the treatment of invasion of the central nervous system
• Prophylactic intrathecal chemotherapy
• Supportive treatment with growth factor products or cytokine
4) Eastern Cooperative Oncology Group performance status (ECOG PS) score 2 or less at the time of registration in the study (refer to “Appendix 1”).
5) Laboratory test results obtained within 14 days before registration in the study meet all of the following requirements:
<table>
<tr><th>Laboratory Parameter</th><th>Requirement</th></tr>
<tr><td>AST</td><td>≤ 2.5 times the upper limit of the institutional reference range</td></tr>
<tr><td>ALT</td><td>≤ 2.5 times the upper limit of the institutional reference range</td></tr>
<tr><td>Total bilirubin</td><td>≤ 1.5 times the upper limit of the institutional reference range</td></tr>
</table></td></tr>
</table>

Serum creatinine	≤ 1.5 times the upper limit of the institutional reference range, or estimated glomerular filtration rate (eGFR) calculated to be ≥ 50 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation
Serum K	Within the institutional reference range*
Serum Ca (corrected for albumin)	Within the institutional reference range*
Serum Mg	Within the institutional reference range*

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

6) Patients who can receive quizartinib orally.
7) Patients who can be hospitalized during the dose-limiting toxicity (DLT) assessment period.

<Exclusion criteria>

1) Diagnosis of acute promyelocytic leukemia
2) Chronic myeloid leukemia in blast crisis (patients with BCR-ABL [breakpoint cluster region- c-Abelson] fusion gene)
3) Diagnosis of treatment-related myeloid tumor
4) Having received other investigational products or having used any investigational medical devices within 30 days before registration in the study.
5) History of malignant tumor except for the following
   - Adequately treated non-melanoma skin cancer
   - Curatively treated mucosal carcinoma or carcinoma in situ with no evidence of relapse for ≥ 2 years after the local treatment
6) History of or current cardiovascular disease as specified below:
   - Heart rate < 50 beats/min, determined as the average of three measurements taken along with 12-lead ECG within 14 days before registration in the study (excluding patients having a cardiac pacemaker)
   - QT corrected for heart rate using Fridericia's method (QTcF) of ≥ 450 ms, determined as the average of three measurements taken within 14 days before registration in the study
   - Diagnosed or suspected congenital long QT syndrome
   - Systolic blood pressure level ≥ 180 mmHg or diastolic

blood pressure level ≥ 110 mmHg within 7 days before registration in the study
- History of clinically significant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, torsade de pointes [TdP], etc.)
- History of Mobitz II atrioventricular block or third degree atrioventricular block (Patients who have a cardiac pacemaker but have not experienced syncope or clinically significant arrhythmia during the period of use are allowed to take part in the study.)
- History of uncontrolled angina pectoris or myocardial infarction within 6 months before registration in the study
- History of Class 3 or more severe heart failure according to "Appendix 2 New York Heart Association (NYHA) Functional Classification"
- History of left ventricular ejection fraction below 45% or the lower limit of the institutional reference range, whichever is lower
- Complete left or right bundle branch block

7) Acute and active infection uncontrolled by antibacterial or antiviral agents or chronic and systemic infection
8) Active and clinically significant liver disease (hepatitis B, hepatitis C, etc.)
9) Tested positive for human immunodeficiency virus (HIV) antibody within 14 days before registration in the study
10) Women confirmed to be pregnant by a pregnancy test performed within 14 days before registration in the study, or breastfeeding women
11) Unwillingness to practice appropriate contraception using effective contraceptive methods (eg, barrier contraceptives combined with spermicides, intrauterine device, etc.) for the entire study period and 3 months after the last dose of the study drug
12) Patients who are otherwise considered ineligible for the

	study in the investigator's or subinvestigator's opinion
Study drug	Quizartinib will be orally administered at the dose listed below once daily every morning under fasting conditions (at least 1 hour before or at least 2 hours after breakfast). Level 1: 20 mg Level 2: 40 mg Remission induction therapy and consolidation therapy will be given for up to 2 cycles and 4 cycles, respectively, each of which is 28 days long. The dose-limiting toxicity (DLT) assessment period is the induction phase. **<Remission induction therapy>** * As an anthracycline drug, either daunorubicin or idarubicin will be chosen, and the same drug will be used in Cycle 1 and Cycle 2. Cycle 1 ("7 + 3") • Cytarabine: 100 mg/m^2/day on Day 1 to Day 7 • Daunorubicin: 60 mg/m^2/day on Day 1 to Day 3 • Idarubicin: 12 mg/m^2/day on Day 1 to Day 3 • Quizartinib: 20 mg/day or 40 mg/day on Day 8 to Day 21 Cycle 2 * The treatment will be administered using the same regimen as in Cycle 1 ("7 + 3") or as shown below ("5 + 2"). • Cytarabine: 100 mg/m^2/day on Day 1 to Day 5 • Daunorubicin: 60 mg/m^2/day on Day 1 to Day 2 • Idarubicin: 12 mg/m^2/day on Day 1 to Day 2 • Quizartinib: 20 mg/day or 40 mg/day on Day 6 to Day 19 **<Consolidation therapy>** • Cytarabine: 3.0 g/m^2/12 hours for patients of < 60 years old and 1.5 g/m^2/12 hours for patients of ≥ 60 years old on Day 1, Day 3, and Day 5 (age at the time of registration in the study) • Quizartinib: 20 mg/day or 40 mg/day on Day 6 to Day 19

Prohibited concomitant drugs and therapies, restricted concomitant drugs, and drugs to be coadministered with care	**<Prohibited concomitant drugs and therapies>** Concomitant use of the following drugs, etc. is prohibited during the quizartinib treatment period. As an exception, the drugs listed in 1) and 2) may be used only when the investigator or subinvestigator considers that these drugs are medically essential to prevent or treat infection. In this case, oral treatment with quizartinib should be interrupted from the start to the end of use of the drugs listed in 1) and 2), and be resumed on the following day of the end of use of the drugs. At the time of resumption, no dose reduction of quizartinib will be necessary unless the investigator or subinvestigator considers it necessary. 1) Drugs that may potentially prolong the QT/corrected QT (QTc) interval 2) Strong cytochrome P450 (CYP) 3A4 inhibitors 3) Strong or moderate CYP3A4 inducers 4) Crude drugs and food products with CYP3A4-inhibiting or -inducing properties (eg, foods and beverages containing St. John's wort or grapefruit) 5) Anticancer treatments other than quizartinib (except hydroxycarbamide) 6) Investigational drugs other than quizartinib, and investigational devices 7) Donor lymphocytes **<Restricted concomitant drugs>** The following treatments should be restricted during oral treatment with quizartinib: • Treatment with hydroxycarbamide for control of the white blood cell count: Restricted to a daily dose of 2 g for up to a total of 14 days **<Drugs to be coadministered with care>** During oral treatment with quizartinib, use of substrates and inhibitors of P-glycoprotein should be avoided as far as possible.
Study procedures	Refer to pages 10 and 13.

Endpoints	Primary	Safety: Adverse event (AEs), laboratory data, vital signs, body weight, 12-lead ECG Pharmacokinetics: Pharmacokinetic parameters of quizartinib and its active metabolite AC886 in plasma
	Secondary	Pharmacodynamics: FMS-like tyrosine kinase (FLT) 3-internal tandem duplication (ITD) status, c-v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) mutation status, phosphorylated FLT3 protein levels in blood, phosphorylated signal transducer and activator of transcription 5 (STAT5) protein levels in blood, phosphorylated c-KIT protein levels in blood, inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein Efficacy: Complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete hematological recovery (CRi), partial remission (PR), no response (NR), composite CR (CRc: CR + CRp + CRi), response rate (CRc + PR)
Primary statistical analyses		Safety evaluation: For AEs that occur or worsen after the start of study treatment, frequency tables will be prepared by event, causality with the study drug or a coadministered drug (cytarabine or an anthracycline drug), and grade according to the Common Terminology Criteria for Adverse Events (CTCAE). DLTs will be assessed by frequency tables. Concerning laboratory data, vital sign measurements, body weight, 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. For QTcF, summary statistics will be calculated, and frequency tables according to the predefined categories will be prepared. Pharmacokinetic evaluation: Concerning plasma concentrations of quizartinib and its active metabolite AC886, summary statistics will be calculated by

	dose level at each time point, and changes in the concentrations will be depicted in figures. Summary statistics of pharmacokinetic parameters will also be calculated. Pharmacodynamic evaluation: Frequency tables will be prepared for the FLT3-ITD status and c-KIT mutation status. For phosphorylated FLT3, STAT5, and c-KIT protein levels in blood and the inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein, the measured values will be summarized at each time point. Efficacy evaluation: Frequency tables for CR, CRp, CRi, PR, and NR will be prepared. The CRc rate, the response rate, and their 95% confidence intervals will be calculated.

Schedule of Study Procedures

Remission Induction Therapy (Up to 2 Cycles)

				Cycle 1										
		Day of Informed Consent	Day of Registration	Day 1	Day 2	Day 3	Day 7	Day 8	Day 9	Day 11	Day 15	Day 21	Day 22	Day 28
Informed consent		●												
Registration of patients			●											
Administration of the study drug and coadministered drugs*														
7 + 3	Quizartinib							←	—	—	—	→		
	Cytarabine			←	—	—	→							
	Daunorubicin or idarubicin			●	●	●								
5 + 2	Quizartinib							←	—	—	—	→		
	Cytarabine			←	—	—	→							
	Daunorubicin or idarubicin			●	●	●								
Baseline subject characteristics		●												
Medical history/complications		●												
Vital sign measurement**		● ≤ 7 days before registration		●a)				●b)	●		●c)	●b)	●	●e)
Body weight		● ≤ 7 days before registration		●a)				●				●		●e)
ECOG PS assessment		● ≤ 7 days before registration		●a)				●				●		●e)
12-lead ECG**		● ≤ 14 days before registration		●a)				●b)	●		●c)	●b)	●	●e)
Laboratory tests (hematology, blood chemistry, urinalysis)**		● ≤ 14 days before registration		●a)				●			●	●		●e)
Pregnancy test		⊙ ≤ 14 days before registration												
Assessment of bone marrow findings (antitumor effect)		● ≤ 14 days before registration										The day ●		
HIV antibody tests		● ≤ 14 days before registration												
Central measurement	Pharmacokinetics							●d)	●		●c)	●d)	●	●
	FLT3-ITD and c-KIT mutations		●a)											
	Phosphorylated protein levels in blood, including FLT3							●b)	●		●	●		
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein							●b)	●		●	●		
Assessment of concomitant drugs and therapies		←		—	—	—	—	—	—	—	—	—	—	—
Monitoring of AEs		←		—	—	—	—	—	—	—	—	—	—	—

		Cycle 2										
		Day 1	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 15	Day 19	Day 21	Day 28
Informed consent												
Registration of patients												
Administration of the study drug and coadministered drugs*												
7 + 3	Quizartinib							←	—	—	→	
	Cytarabine	←	—	—	—	—	→					
	Daunorubicin or idarubicin	●	●	●								
5 + 2	Quizartinib					←	—	—	—	→		
	Cytarabine	←	—	—	→							
	Daunorubicin or idarubicin	●	●									
Baseline subject characteristics												
Medical history/complications												
Vital sign measurement**		●a)!				5+2 ●c)		7+3 ●c)	●	5+2 ●	7+3 ●	●e)
Body weight		●a)!										●e)
ECOG PS assessment		●a)!				5+2 ●		7+3 ●		5+2 ●	7+3 ●	●e)
12-lead ECG**		●a)!				5+2 ●c)		7+3 ●c)	●	5+2 ●	7+3 ●	●e)
Laboratory tests (hematology, blood chemistry, urinalysis)**		●a)!				5+2 ●		7+3 ●	●	5+2 ●	7+3 ●	●e)
Pregnancy test												
Assessment of bone marrow findings (antitumor effect)											The day ●	
HIV antibody tests												
Central measurement	Pharmacokinetics											
	FLT3-ITD and c-KIT mutations											
	Phosphorylated protein levels in blood, including FLT3											
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein											
Assessment of concomitant drugs and therapies		→	→	→	→	→	→	→	→	→	→	→
Monitoring of AEs		→	→	→	→	→	→	→	→	→	→	→

● Mandatory, ○ To be performed only in selected patients

a) Before the start of administration of cytarabine and the anthracycline drug
b) Pre-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
c) Pre-dose, 2 hours (±10 minutes) post-dose, and 4 hours (±10 minutes) post-dose
d) Pre-dose, 30 minutes (±10 minutes) post-dose, 1 hour (±10 minutes) post-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
e) −3 days to the day

* Remission induction therapy in Cycle 2 will be given using the same regimen as in Cycle 1 ("7 + 3") or on the dosing schedule ("5 + 2") shown in the table.

** If drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors are used after the start of quizartinib treatment, quizartinib treatment should be interrupted from the start to the end of use of these drugs.
After the day when quizartinib is resumed, the following procedures will be performed at the time points listed below:

[1]	Pre-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement, 12-lead ECG, and laboratory tests
[2]	2 hours (±10 minutes) post-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement and 12-lead ECG
[3]	Pre-dose of quizartinib on Day 4 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[4]	Pre-dose of quizartinib on Day 8 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[5]	Pre-dose of quizartinib on Day 11 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[6]	Pre-dose of quizartinib on Day 15 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG

! If Cycle 2 is started within +7 days reckoned from Day 28 of Cycle 1, the procedures scheduled on Day 1 of Cycle 2 are not necessary.

Schedule of Study Procedures

Consolidation Therapy (Up to 4 Cycles)

			Cycle 1								
		Before the Start of Treatment	Day 1	Day 3	Day 5	Day 6	Day 7	Day 13	Day 19	Day 21	Day 28
Informed consent		●									
Registration of patients											
Administration of the study drug and coadministered drugs											
	Quizartinib					←	—	—	→		
	Cytarabine		●●	●●	●●						
Baseline subject characteristics											
Medical history/complications											
Vital sign measurement**			●a)			●b)		●c)	●		●d)
Body weight			●a)			●			●		●d)
ECOG PS assessment			●a)			●			●		●d)
12-lead ECG**			●a)			●b)		●c)	●		●d)
Laboratory tests (hematology, blood chemistry, urinalysis)**			●a)			●		●	●		●d)
Pregnancy test		⊙ Within 7 days before treatment									
Assessment of bone marrow findings (antitumor effect)										The day ●	
HIV antibody tests											
Central measurement	Pharmacokinetics					●c)	●	●c)	●		●d)
	FLT3-ITD and c-KIT mutations										
	Phosphorylated protein levels in blood, including FLT3										
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein										
Assessment of concomitant drugs and therapies		←	—	—	—	—	—	—	—	—	→
Monitoring of AEs		←	—	—	—	—	—	—	—	—	→

		Cycle 2 and Thereafter									
		Day 1	Day 3	Day 5	Day 6	Day 13	Day 19	Day 21	Day 28	At Withdrawal	Post-treatment Observation
Informed consent											
Registration of patients											
Administration of the study drug and coadministered drugs											
	Quizartinib				←	—	→				
	Cytarabine	●●	●●	●●							
Baseline subject characteristics											
Medical history/complications											
Vital sign measurement**		●a) !			●	●	●		●d)	●e)	●f)
Body weight		●a) !							●d)	●e)	●f)
ECOG PS assessment		●a) !			●		●		●d)	●e)	●f)
12-lead ECG**		●a) !			●	●	●		●d)	●e)	●f)
Laboratory tests (hematology, blood chemistry, urinalysis)**		●a) !			●	●	●		●d)	●e)	●f)
Pregnancy test											
Assessment of bone marrow findings (antitumor effect)								The day ●		●e)	
HIV antibody tests											
Central measurement	Pharmacokinetics										
	FLT3-ITD and c-KIT mutations										
	Phosphorylated protein levels in blood, including FLT3										
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein										
Assessment of concomitant drugs and therapies		→									
Monitoring of AEs		→									

● Mandatory, ○ To be performed only in selected patients

a) Before the start of cytarabine administration
b) Pre-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
c) Pre-dose, 2 hours (±10 minutes) post-dose, and 4 hours (±10 minutes) post-dose
d) −3 days to the day
e) Day when study termination is decided (−3 days to +7 days)
f) 28th day (±7 days) reckoned from the day of the last dose of the study drug

** If drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors are used after the start of quizartinib treatment, quizartinib treatment should be interrupted from the start to the end of use of these drugs.
After the day when quizartinib is resumed, the following procedures will be performed at the time points listed below:

[1]	Pre-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement, 12-lead ECG, and laboratory tests
[2]	2 hours (±10 minutes) post-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement and 12-lead ECG
[3]	Pre-dose of quizartinib on Day 4 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[4]	Pre-dose of quizartinib on Day 8 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[5]	Pre-dose of quizartinib on Day 11 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[6]	Pre-dose of quizartinib on Day 15 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG

! If the next cycle is started within +7 days reckoned from Day 28 of each cycle, the procedures scheduled on Day 1 of the next cycle are not necessary.

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List of Abbreviations and Definitions of Terms

List of Abbreviations

Abbreviation	Full Expression
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	L-alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	L-aspartate aminotransferase
BCR-ABL	breakpoint cluster region- c-Abelson
BUN	blood urea nitrogen
CR	complete remission
CRc	composite CR
CRi	CR with incomplete hematological recovery
CRp	CR with incomplete platelet recovery
CRP	C-reactive protein
CSF1R	colony stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDR	discoidin domain receptor tyrosine kinase
DFS	disease free survival
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capturing
eGFR	estimated glomerular filtration rate
FLT	FMS-like tyrosine kinase
GCP	Good Clinical Practice
γ-GT	γ-glutamyl transferase
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IC_{50}	50% inhibitory concentration
$I_{Ca\text{-}L}$	long-lasting calcium current
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
I_{Kr}	potassium current carried by channel formed from hERG subunits
I_{Ks}	potassium current carried by channel formed from KVLQT1 (KCNQ1) subunits and minK (KCNE1) b-subunits
I_{Na}	sodium current
IRB	Institutional Review Board
ITD	internal tandem duplication
KDM	kinase domain mutation
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
LDH	lactic acid (lactate) dehydrogenase
MAPK	mitogen-activated protein kinase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose

Abbreviation	Full Expression
NCCN	The National Comprehensive Cancer Network
NYHA	New York Heart Association
NR	no response
PDGFR	platelet-derived growth factor receptor
PI3K	phosphatidylinositol 3-kinase
PR	partial remission
PS	performance status
PT	prothrombin time
PT-INR	prothrombin time-international normalized ratio
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
RTK	receptor tyrosine kinase
SAVER	Serious Adverse Event Report
STAT5	signal transducer and activator of transcription 5
TdP	torsades de pointes
TEAE	treatment emergent adverse event
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization
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)-6)]

FMS-like tyrosine kinase (FLT) 3 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)]

Quizartinib (Development Code: AC220) is an FLT3 inhibitor developed by Ambit Biosciences Corporation that has higher selectivity and affinity for FLT3 than first generation FLT3 inhibitors (lestauritinib, tandutinib, midostaurin, sorafenib, sunitinib, etc.). Nonclinical data have demonstrated that quizartinib is a potent and specific inhibitor of FLT3 kinase and several other Class III RTKs (KIT, CSF1R/FMS, RET, and PDGFRα/β) and that it has antitumor activity against FLT3-ITD positive human leukemia cells. Overseas Phase 2 studies have also demonstrated high efficacy of quizartinib in relapsed or refractory AML patients. It is therefore expected that quizartinib will become a new treatment option not only for patients with relapsed or refractory AML, but also for patients with initially diagnosed AML. Due to its selective FLT3 inhibitory activity, quizartinib is also expected to improve the treatment results in a selected population of FLT3-ITD positive AML patients, who are known to have poor prognosis. Against this background, quizartinib received fast track designation in November 2010 in the US. At present, a global Phase 3 study is ongoing mainly in Europe and the US.

In Japan, relapsed or refractory AML patients 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.[8)] There are also no molecular targeting drugs that can be used for initially-diagnosed AML patients, in whom a high relapse rate is still a problem. In view of this situation, Daiichi Sankyo decided to participate in the Japanese development of quizartinib for AML patients.

1.2 Nonclinical Study Data

1.2.1 Pharmacology

In a biochemical binding assay using a panel of 441 kinases, quizartinib and its metabolite, AC886, exhibited the highest binding affinity for FLT3 (dissociation constant: 1.3 nM for quizartinib and 0.54 nM for AC886). The binding affinity for other

Class III RTKs (eg, KIT, CSF1R/FMS, PDGFRβ, and RET) was within 10-fold lower than that for FLT3, and the binding affinity for 4 additional kinases (FLT1, FLT4, discoidin domain receptor tyrosine kinase [DDR] 1, PDGFRα, and vascular endothelial growth factor receptor [VEGFR] 2) was within 100-fold lower than that for FLT3. On the other hand, quizartinib showed a weak inhibitory activity against 118 different enzymes, receptor channels, and transporters, and the 50% inhibitory concentration (IC_{50}) was higher than 1 μM.

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 (IC_{50}: approximately 0.3 nM for quizartinib and 0.26 nM for AC886). 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.

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; however, no hemodynamic or ECG changes were seen at 3 mg/kg. In the assessment of potential effects of quizartinib and AC886 on potassium current carried by channel formed from hERG subunits (I_{Kr}) channel-coded by hERG using a patch clamp approach in HEK293 cells overexpressing human ether-à-go-go related gene (hERG), quizartinib did not inhibit the I_{Kr} channel, whereas AC886 inhibited the I_{Kr} channel concentration-independently (maximal inhibition: 30% to 40%). In the assessment of potential effects of quizartinib and AC886 on sodium current (I_{Na}), potassium current carried by the channel formed by KVLQT1 (KCNQ1) subunits and minK (KCNE1) b-subunits (I_{Ks}), and long-lasting calcium current ($I_{Ca\text{-}L}$), quizartinib inhibited I_{Ks}, and AC886 inhibited I_{Na}, I_{Ks}, and $I_{Ca\text{-}L}$. In ex vivo studies using rabbit heart preparations, quizartinib and AC886 caused increases in QTc interval at concentrations of > 3 μM. It was thus suggested that the effects of the two compounds on potassium currents (I_{Ks} + I_{Kr}) would play a role in QTc prolongation.

1.2.2 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 P-glycoprotein, 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.

1.2.3 Toxicology

Quizartinib was tested in single-dose 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 (rat), 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 (RBC) and white blood cell (WBC) 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. 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.[9),10),11)] However, a review of the assay data in accordance with the guidance on photosafety evaluation of pharmaceuticals issued on 21 May 2014[12)] resulted in the conclusion that quizartinib is not phototoxic.

1.3 Clinical Study Data

1.3.1 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.

1.3.2 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 of ≥ 60 years old with relapsed or refractory AML after 1 first-line chemotherapy regimen were enrolled in Cohort 1, while AML patients of ≥ 18 years old 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 = CR + [CR with incomplete hematological recovery; CRi] + [CR with incomplete platelet recovery; CRp]) rate was 52% in a subset of FLT3-ITD positive patients, with a median overall survival of 25.3 weeks. In Cohort 2, the CRc rate was 45% in a subset of FLT3-ITD positive patients, with a median overall survival of 22.9 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 AML patients, 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 1.3-1). The study also demonstrated that the CRc rates were comparable to those observed in Study AC220-002 (Table 1.3-2). 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 gastrointestinal disorders (eg, nausea, diarrhea, and vomiting), hematotoxicities (eg, anemia, neutropenia, and thrombocytopenia), febrile neutropenia, fever, fatigue, and QTc prolongation. 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 1.3-1 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			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%	50%	44%
> 30, ≤ 60	46%	51%	8%	47%	36%
> 60	46%	39%	92%	3%	19%

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

Table 1.3-2 Composite Complete Remission and Partial Response Rates in Two Phase 2 Studies

Daily Dose of Quizartinib	Study AC220-002			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%

1.3.3 Phase 1b Study (Study 2689-CL-2005)

In this study, quizartinib was administered in combination with induction and consolidation chemotherapy in initially diagnosed AML patients and the safety and pharmacokinetics were assessed. During the induction phase, cytarabine (200 mg/m^2/day on Day 1 to Day 7), daunorubicin (60 mg/m^2/day on Day 1 to Day 3), and quizartinib (40 mg/day or 60 mg/day on Day 4 to Day 10 or Day 4 to Day 17) were administered for up to 2 cycles. During the consolidation phase, cytarabine (3.0 g/m^2/12 hours on Day 1, Day 3, and Day 5) and quizartinib (40 mg/day or 60 mg/day on Day 4 to Day 10 or Day 4 to Day 17) were administered for up to 3 cycles.
AEs frequently reported in the study were nausea, diarrhea, constipation, hypokalemia, hypomagnesemia, neutropenia, vomiting, fatigue, headache, hypophosphatemia, hypotension, pyrexia, and rash. One patient had a fatal outcome due to cardiac arrest after experiencing serious AEs (SAEs) (mucosal inflammation, pleural effusion, and pericardial effusion); however, the causality between cardiac arrest and quizartinib was ruled out.

1.3.4 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/day to 90 mg/day. 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.

1.4 Known and Foreseeable Risks

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), 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 from Study AC220-002 indicate delayed recovery of ANC and platelets as a consequence of continued treatment with quizartinib in many patients.

SAEs related to bone marrow depression (eg, febrile bone marrow aplasia, 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 "1.3.2 Phase 2 Studies (Studies AC220-002 and 2689-CL-2004)." Treatment with quizartinib may induce TdP depending on the extent of QTc prolongation, concomitant administration of QTc prolonging drugs, a history of TdP, preexisting QTc prolongation, congenital long QT syndrome, congestive heart failure, 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.

Chemotherapy used in this study consists of remission induction therapy and consolidation therapy given for up to 2 cycles and 4 cycles, respectively, each of which is 28 days long.

During the induction phase, quizartinib will be administered in combination with cytarabine and an anthracycline drug (either daunorubicin or idarubicin will be chosen). In Cycle 1, the treatment will be administered as cytarabine at a dose of 100 mg/m^2/day on Day 1 to Day 7, daunorubicin at a dose of 60 mg/m^2/day or idarubicin at a dose of 12 mg/m^2/day on Day 1 to Day 3, and quizartinib at a dose of 20 mg/day or 40 mg/day on Day 8 to Day 21. In Cycle 2, the treatment will be administered by the same dosing

schedule as in Cycle 1 or as cytarabine at a dose of 100 mg/m^2/day on Day 1 to Day 5, daunorubicin at a dose of 60 mg/m^2/day or idarubicin at a dose of 12 mg/m^2/day on Day 1 to Day 2, and quizartinib on Day 6 to Day 19. The anthracycline drug used in Cycle 2 has to be the same as that in Cycle 1. The daily dose of daunorubicin used in this study exceeds the daily dose approved in Japan (the dosage approved in Japan is 0.4 mg/kg/day to 1.0 mg/kg/day given for 3 to 5 consecutive days or every other day, which is calculated to be 24 mg to 60 mg/day for patients weighing 60 kg; however, the daily dose in this study is 96 mg per 1.6 m^2). It has not been reported to date whether there is any difference in the safety between the dose used in this study and the dose recommended in Japan.

During the consolidation phase, cytarabine and quizartinib will be administered. The cytarabine dose is 3.0 g/m^2/12 hours for AML patients of < 60 years old (1.5 g/m^2/12 hours for AML patients of ≥ 60 years old) given on Day 1, Day 3, and Day 5. Quizartinib will be administered at a dose of 20 mg/day or 40 mg/day on Day 6 to Day 19. Cytarabine, which is used as consolidation therapy in Japan, will be administered on Day 1 to Day 5 at a dose of 2.0 g/m^2/12 hours for young AML patients and at a lower dose for elderly AML patients at the investigator's discretion. This is because cytarabine has been confirmed to be effective at a dose of 3.0 g/m^2 in patients of < 60 years old; however, the regimen is considered to involve frequent central nervous system (CNS)-related complications (attacks, cerebral dysfunction, and acute cerebellar syndrome).[1),13)] Cytarabine may cause CNS complications, and caution is therefore required in this study.

1.5 Rationale for the Dosage

This study will be conducted to confirm the safety of quizartinib in combination with standard chemotherapy, which is specified in a global Phase 3 study that is currently underway abroad in patients with initially diagnosed FLT3-ITD-positive AML (AC220-A-U302: QuANTUM-First), in Japanese AML patients, and then to assess and determine whether Japan's participation in the above study is possible or not. For this reason, the dosage regimen of chemotherapy and quizartinib used in this study was set based on the dosage regimen of induction and consolidation therapy used in QuANTUM-First.

The guideline for the management of AML (Version 1, 2015) by The National Comprehensive Cancer Network (NCCN) recommends, as one of the remission induction regimens, the use of cytarabine (100 mg/m^2/day to 200 mg/m^2/day) for 7 consecutive

days and an anthracycline drug (daunorubicin at 45 mg/m^2/day to 90 mg/m^2/day or idarubicin at 12 mg/m^2/day) for 3 consecutive days. As far as the daunorubicin dose is concerned, there is a report that complete remission (CR) rate and overall survival were more favorable with 90 mg/m^2/day given for 3 days than with 45 mg/m^2/day given for 3 days in initially diagnosed AML patients of < 60 years old.[14] On the other hand, in a clinical study in which cytarabine (100 mg/m^2/12 hours) was administered consecutively on Day 1 to Day 10 and daunorubicin (90 mg/m^2/day or 60 mg/m^2/day) was administered for 3 days on Day 1, Day 3, and Day 5 in untreated AML patients or high-risk myelodysplastic syndrome (MDS) patients, no difference in the CR rate was observed between the 90 mg/m^2/day and 60 mg/m^2/day groups; however, the 60-day mortality was higher in the 90 mg/m^2/day group (10% vs 5%). The 2-year survival was almost the same between the treatment groups (59% vs 60%).[15] Based on these, QuANTUM-First adopted remission induction therapy as cytarabine (100 mg/m^2/day) given continuously on Day 1 to Day 7 and an anthracycline drug (daunorubicin at 60 mg/m^2/day or idarubicin at 12 mg/m^2/day) given consecutively on Day 1 to Day 3. The dosage of daunorubicin approved in Japan is 0.4 mg/kg/day to 1.0 mg/kg/day given for 3 to 5 consecutive days or every other day, and the daily dose is calculated to be 24 mg/day to 60 mg/day for patients weighing 60 kg. The dose of 60 mg/m^2/day used in this study is 96 mg/day per 1.6 m^2.

The NCCN guideline for the management of AML (Version 1, 2015) recommends, as one of the postremission regimens, high-dose cytarabine (2 g/m^2/12 hours to 3 g/m^2/12 hours for patients of < 60 years old and 1 g/m^2/12 hours to 1.5 g/m^2/12 hours for patients of ≥ 60 years old) given a total of 6 times on Day 1, Day 3 and Day 5. On the other hand, European LeukemiaNet recommends the use of high-dose cytarabine as consolidation therapy in clinical studies only.[16] At present, consolidation therapy recommended for AML patients with FLT3-ITD mutations has not been clarified. The NCCN guideline recommends participation in clinical studies, whereas European LeukemiaNet recommends HSCT for patients of 18 to 60 years old and low-dose cytarabine as consolidation therapy for patients of ≥ 60 years old.[16] In a clinical study in which remission induction therapy with cytarabine and daunorubicin was given to initially diagnosed AML patients, and three dosage regimens of cytarabine (5-day continuous treatment at a dose of 100 mg/m^2/day, 5-day continuous treatment at a dose of 400 mg/m^2/day, or a total of 6-dose treatment at 3 g/m^2/12 hours on Day 1, Day 3, and Day 5) were compared in patients achieving CR, disease-free survival (DFS) in patients of < 60 years old was significantly higher in the 3 g/m^2/12 hours group than in the

100 mg/m^2/day and 400 mg/m^2/day groups.[13)] Therefore, QuANTUM-First adopted, as consolidation therapy, cytarabine given at a dose of 3 g/m^2/12 hours a total of 6 times on Day 1, Day 3, and Day 5 for patients of < 60 years old and cytarabine given at a dose of 1.5 g/m^2/12 hours a total of 6 times on Day 1, Day 3, and Day 5 for patients of ≥ 60 years old. The cytarabine dosage approved for patients of < 60 years old in Japan is 2 g/m^2 given every 12 hours for a maximum of 6 consecutive days, and the daily dose of cytarabine used in this study exceeds the daily dose of cytarabine approved in Japan.

2. STUDY OBJECTIVES

Primary objective:

To evaluate the safety and pharmacokinetics of quizartinib in combination with standard induction and consolidation therapy in Japanese patients with initially diagnosed AML, and to determine the dose for subsequent phases of development.

Secondary objectives:

- Exploratory study of quizartinib-related biomarkers
- Exploratory evaluation of antitumor effect

3. STUDY DESIGN

This study is designed as a multicenter, open-label, Phase 1 clinical study of quizartinib at 20 mg or 40 mg administered in combination with chemotherapy.

Quizartinib will be administered at a dose of 20 mg at Level 1 and 40 mg at Level 2. Dose escalation within a single patient is not allowed. The chemotherapy regimen coadministered with quizartinib is shown in "Figure 3-1 Study Flow."

The presence or absence of dose-limiting toxicity (DLT) of quizartinib will be checked at each level based on the definition provided in "5.4.1 Definition of Dose-limiting Toxicities," and the MTD will be determined using the algorithm of a 3 + 3 design (refer to Section "5.4.2 Assessment Method").

The DLT assessment period is the induction phase; the presence or absence of DLT during the above period will be confirmed in a minimum of 3 patients (including at least 1 patient of < 60 years old at the time of registration in the study) at each level. If DLT occurs, additional patients will be enrolled at the concerned level in accordance with "Table 5.4-1 Criteria for Proceeding to Level 2" or " Table 5.4-2 Criteria for Assessing Maximum Tolerated Doses (MTDs) at Level 2," or quizartinib dose escalation will be discontinued. If DLT cannot be assessed appropriately in any patient, additional patients will be enrolled in accordance with "5.4.4 Enrollment of Additional Patients."

Figure 3-1 Study Flow

Remission induction therapy

<Cycle 1>
Day 1 to Day 7: Continuous intravenous infusion of cytarabine (100 mg/m^2/day)
Day 1 to Day 3: Intravenous infusion of daunorubicin (60 mg/m^2/day) or idarubicin (12 mg/m^2/day)
Day 8 to Day 21: Oral administration (once daily) of quizartinib (20 mg/day or 40 mg/day)

Bone marrow aspiration or biopsy will be performed on Day 21 of Cycle 1; if myeloblasts account for < 5%, the treatment will proceed to Cycle 1 of consolidation therapy; if myeloblasts account for ≥ 5%, remission induction therapy in Cycle 2 will be given.

<Cycle 2> Treatment will be given using the same regimen as in Cycle 1 or as shown below.
Day 1 to Day 5: Continuous intravenous infusion of cytarabine (100 mg/m^2/day)
Day 1 to Day 2: Intravenous infusion of daunorubicin (60 mg/m^2/day) or idarubicin (12 mg/m^2/day)
Day 6 to Day 19: Oral administration (once daily) of quizartinib (20 mg/day or 40 mg/day)

⇩

Consolidation therapy

<Cycle 1>
Day 1, 3, 5: Intravenous infusion of cytarabine (3.0 g/m^2/12 hours for patients of < 60 years old and 1.5 g/m^2/12 hours for patients of ≥ 60 years old)
Day 6 to Day 19: Oral administration (once daily) of quizartinib (20 mg/day or 40 mg/day)

Consolidation therapy will be given for up to 4 cycles in patients with confirmed tolerability.

<Cycle 2 and thereafter> Same regimen as in Cycle 1.
Patients achieving CR, CRp, or CRi in Cycle 2 or later are allowed to terminate consolidation therapy and undergo hematopoietic stem cell transplant.

<Rationale>

In order to confirm the tolerability of remission induction therapy and consolidation therapy, which are specified in QuANTUM-First, which is currently underway in patients with initially diagnosed FLT3-ITD-positive AML, in Japanese patients with initially diagnosed AML, it was decided to use the same remission induction therapy and consolidation therapy as in QuANTUM-First in this study too.

In QuANTUM-First, quizartinib is administered at 20 mg to 40 mg in combination with standard remission induction and consolidation therapy. The quizartinib dose was therefore set as 20 mg at Level 1 and 40 mg at Level 2 in this study.

In this study, DLT of quizartinib will be assessed during the induction phase; however, safety data collected from each patient during the consolidation phase will also be used to decide whether Japan can participate in QuANTUM-First or not.

4. STUDY POPULATION

4.1 Selection of Patients

Patients who meet all of the inclusion criteria and do not fit any of the following exclusion criteria are eligible for the study.

4.1.1 Inclusion Criteria

1) Provision of written informed consent for participation in the study.
2) Age ≥ 20 years and ≤ 75 years at the time of registration in the study
3) AML patients (including those with a history of MDS) who have not previously received other treatments (including quizartinib) than those listed below
   - Leukapheresis
   - Treatment with hydroxycarbamide for control of the white blood cell count
   - Cranial radiation for the treatment of invasion of the central nervous system
   - Prophylactic intrathecal chemotherapy
   - Supportive treatment with growth factor products or cytokine
4) Eastern Cooperative Oncology Group performance status (ECOG PS) score 2 or less at the time of registration in the study (refer to "Appendix 1").
5) Laboratory test results obtained within 14 days before registration in the study 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) calculated to be ≥ 50 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation
Serum K	Within the institutional reference range*
Serum Ca (corrected for albumin)	Within the institutional reference range*
Serum Mg	Within the institutional reference range*

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

6) Patients who can receive quizartinib orally.
7) Patients who can be hospitalized during the DLT assessment period.

<Rationale>

1) 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. The upper age limit was set at 75 years as in QuANTUM-First.

3), 4), 6), 7) To evaluate the safety of quizartinib in an appropriate manner.

5) 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.[17)]

4.1.2 Exclusion Criteria

1) Diagnosis of acute promyelocytic leukemia
2) Chronic myeloid leukemia in blast crisis (patients with BCR-ABL [breakpoint cluster region- c-Abelson] fusion gene)
3) Diagnosis of treatment-related myeloid tumor
4) Having received other investigational products or having used any investigational medical devices within 30 days before registration in the study.
5) History of malignant tumor except for the following
   - Adequately treated non-melanoma skin cancer
   - Curatively treated mucosal carcinoma or carcinoma in situ with no evidence of relapse for ≥ 2 years after the local treatment
6) History of or current cardiovascular disease as specified below:
   - Heart rate < 50 beats/min, determined as the average of three measurements taken along with 12-lead ECG within 14 days before registration in the study (excluding patients having a cardiac pacemaker)
   - QT corrected for heart rate using Fridericia's method (QTcF) of ≥ 450 ms, determined as the average of three measurements taken within 14 days before registration in the study
   - Diagnosed or suspected congenital long QT syndrome
   - Systolic blood pressure level ≥ 180 mmHg or diastolic blood pressure level ≥ 110 mmHg within 7 days before registration in the study
   - History of clinically significant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, TdP, etc.)
   - History of Mobitz II atrioventricular block or third degree atrioventricular block (Patients who have a cardiac pacemaker but have not experienced syncope or clinically significant arrhythmia during the period of use are allowed to take part in the study.)
   - History of uncontrolled angina pectoris or myocardial infarction within 6 months before registration in the study
   - History of Class 3 or more severe heart failure according to "Appendix 2 New

York Heart Association (NYHA) Functional Classification"

- History of left ventricular ejection fraction below 45% or the lower limit of the institutional reference range, whichever is lower
- Complete left or right bundle branch block

7) Acute and active infection uncontrolled by antibacterial or antiviral agents or chronic and systemic infection
8) Active and clinically significant liver disease (hepatitis B, hepatitis C, etc.)
9) Tested positive for human immunodeficiency virus (HIV) antibody within 14 days before registration in the study
10) Women confirmed to be pregnant by a pregnancy test performed within 14 days before registration in the study, or breastfeeding women
11) Unwillingness to practice appropriate contraception using effective contraceptive methods (eg, barrier contraceptives combined with spermicides, intrauterine device, etc.) for the entire study period and 3 months after the last dose of the study drug
12) Patients who are otherwise considered ineligible for the study in the investigator's or subinvestigator's opinion

<Rationale>

1) to 9) To evaluate the safety of quizartinib in an appropriate manner.
10), 11) Established because effects of quizartinib on the fetus and nursing babies cannot be ruled out.
12) Established so that the investigator or subinvestigator can determine the eligibility for participation in the study from a comprehensive standpoint with careful consideration for patient safety.

4.1.3 Registration of Patients

Patients will be registered in the study according to the procedures described below.

4.1.3.1 Patient Registration Procedure

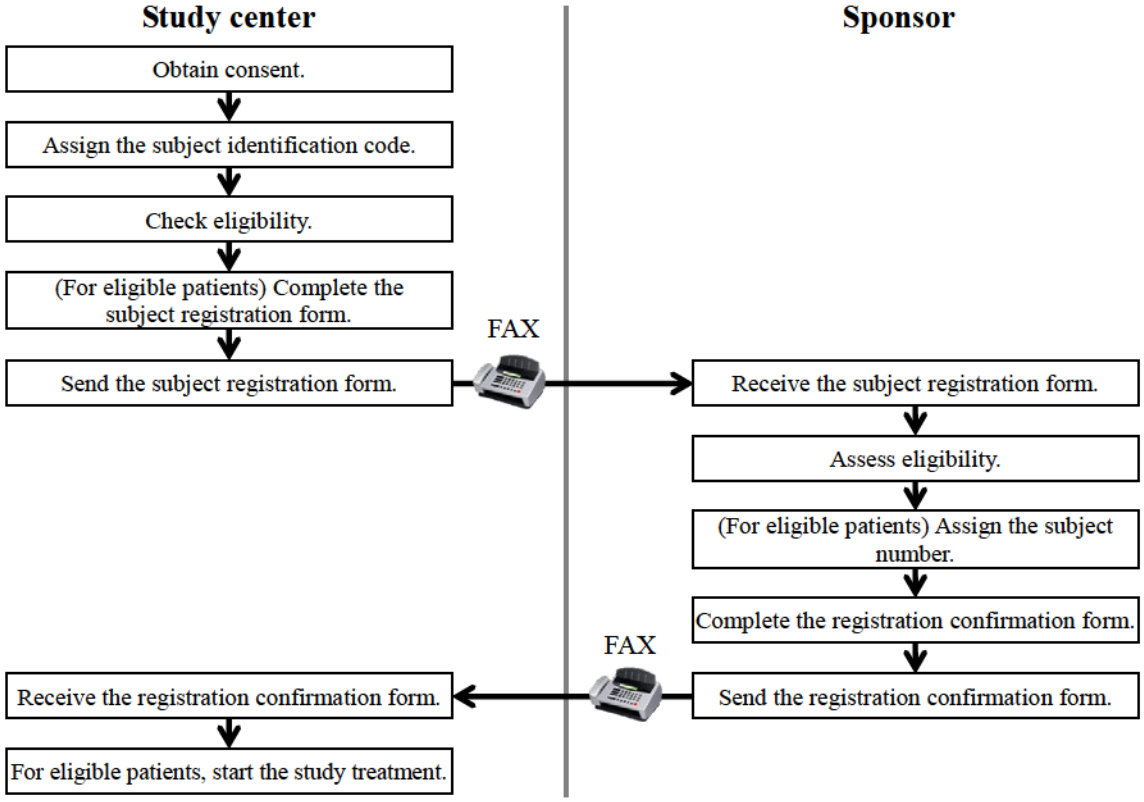
After obtaining written informed consent from each patient, the investigator or subinvestigator will assign a subject identification code to the patient. If the above-stated patient is assessed to be eligible for the study, the investigator or subinvestigator will enter the necessary information on the patient in the subject registration form (Attachment 1) 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 investigator or subinvestigator 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 investigator or subinvestigator 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: PPD
TEL: PPD

The investigator or subinvestigator 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 investigator or subinvestigator 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 investigator or subinvestigator 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 investigator or subinvestigator later confirms that the patient meets the eligibility criteria, the investigator or subinvestigator may again obtain consent for participation in the study from the patient and fax the subject registration form to the sponsor.

Figure 4.1-1 Patient Registration Procedure



4.1.3.2 Notifying Any Other Physicians Treating Patients of Their Study Participation

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 information in the medical record.

4.2 Subject Withdrawal Criteria and Procedures

If a patient meets the criteria specified in "5.6 Withdrawal Criteria," the investigator or subinvestigator will withdraw the patient from study treatment and perform the examinations and assessments according to "6.4 At the Time of Withdrawal from the Study." The investigator or subinvestigator will record the date of withdrawal, reason for withdrawal, and examination/assessment results in the case report form (CRF).

5. METHODOLOGY

5.1 Study Drug

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 AC010220·HCl.
4) Lot number: Lot numbers are listed in the "Study Drug Management Procedures."

5.1.1 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 5.1-1 Information Displayed on the Study Drug Label."

Table 5.1-1 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

5.1.2 Storage of the Study Drug

After concluding the clinical study contract with the study center, the sponsor will distribute the study drug to the study center. The study drug manager will store and manage the study drug at ≤ 25°C without freezing. The study drug will be managed and retrieved in accordance with the "Study Drug Management Procedures."

5.2 Coadministered Drugs (Cytarabine and Anthracycline Drugs)

In this study, cytarabine and anthracycline drugs (daunorubicin or idarubicin) will be used as coadministered drugs. For the details and handling of coadministered drugs,

refer to the package insert (Protocol Attachment), etc.

5.2.1 Cytarabine

1) Content and dosage form: A clear colorless aqueous solution for injection (Cylocide Injection: pH 7.5 to 9.0; Cylocide N Injection: pH 8.0 to 9.3). The content is shown below.

Specification	Content
1 mL ampoule	20 mg of cytarabine and 9 mg of sodium chloride
2 mL ampoule	40 mg of cytarabine and 18 mg of sodium chloride
3 mL ampoule	60 mg of cytarabine and 27 mg of sodium chloride
5 mL ampoule	100 mg of cytarabine and 45 mg of sodium chloride
10 mL ampoule	200 mg of cytarabine and 90 mg of sodium chloride
20 mL ampoule	400 mg of cytarabine and 180 mg of sodium chloride
50 mL vial	1 g of cytarabine and 450 mg of sodium chloride

* Sodium chloride is an inactive ingredient.

5.2.2 Daunorubicin

1) Content and dosage form: Red lyophilized formulation (pH 5.0 to 6.5) that contains 20 mg of daunorubicin hydrochloride and 100 mg of D-Mannitol as an inactive ingredient per vial.

5.2.3 Idarubicin

1) Content and dosage form: Yellow-red lyophilized formulation (pH 5.0 to 7.0) that contains 5 mg of idarubicin hydrochloride and 50 mg of lactose hydrate as an inactive ingredient per vial.

5.3 Treatment Method of the Study Drug and Coadministered Drugs (Cytarabine and Anthracycline Drugs)

5.3.1 Dose and Regimen

Quizartinib will be orally administered at the dose listed below once daily every morning under fasting conditions (at least 1 hour before or at least 2 hours after breakfast).

Table 5.3-1 Quizartinib Dose

Level	Dose
1	20 mg
2	40 mg

If a patient vomits after taking a dose of quizartinib, a replacement dose may not be given on the same day. A patient who did not take quizartinib at the usual hour of dosing (eg,

forgot to take the dose) will be allowed to take the missed dose at least 1 hour before or at least 2 hours after a meal within about 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 until around 18:00). A patient who did not take the missed dose within about 10 hours after the usual hour of dosing should not take quizartinib on that day, and resume taking quizartinib on the following day. The patient may not take two doses at once on the day when the drug is resumed.

Remission induction therapy and consolidation therapy will be given for up to 2 cycles and 4 cycles, respectively, each of which is 28 days long.

Remission Induction Therapy

* As an anthracycline drug, either daunorubicin or idarubicin will be chosen, and the same drug will be used in Cycle 1 and Cycle 2.

Cycle 1 ("7 + 3")

- Cytarabine: Cytarabine, which is diluted with 5% glucose solution or 5% normal saline to make a total volume of 250 mL to 500 mL, will be administered at a daily dose of 100 mg/m^2 by 24-hour continuous intravenous infusion for 7 consecutive days on Day 1 to Day 7.
- Daunorubicin: Daunorubicin, which is dissolved in 10 mL of Japanese Pharmacopoeia (JP) sterile water for injection per vial, will be administered at a daily dose of 60 mg/m^2 by intravenous infusion over a period of 30 to 60 minutes on Day 1 to Day 3.
- Idarubicin: Idarubicin, which is dissolved in 5 mL of JP sterile water for injection per vial, will be administered at a daily dose of 12 mg/m^2 by intravenous infusion over a period of 30 to 60 minutes on Day 1 to Day 3.
- Quizartinib: After the end of cytarabine administration, quizartinib will be orally administered at a dose of 20 mg or 40 mg once daily on Day 8 to Day 21.

Cycle 2

* The treatment will be administered using the same regimen as in Cycle 1 ("7 + 3") or as shown below ("5 + 2").

- Cytarabine: Cytarabine, which is diluted with 5% glucose solution or 5% normal saline to make a total volume of 250 mL to 500 mL, will be

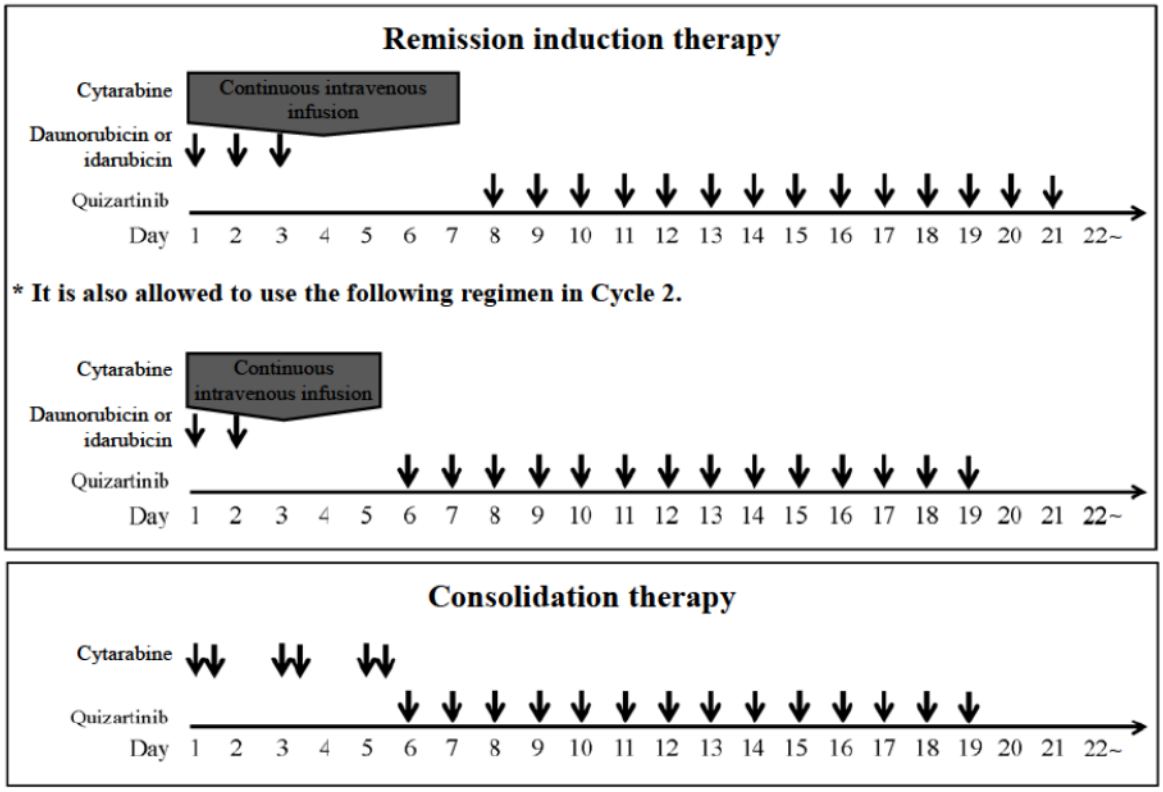
administered at a daily dose of 100 mg/m^2 by 24-hour continuous intravenous infusion for 5 consecutive days on Day 1 to Day 5.

- Daunorubicin: Daunorubicin, which is dissolved in 10 mL of JP sterile water for injection per vial, will be administered at a daily dose of 60 mg/m^2 by intravenous infusion over a period of 30 to 60 minutes on Day 1 to Day 2.
- Idarubicin: Idarubicin, which is dissolved in 5 mL of JP sterile water for injection per vial, will be administered at a daily dose of 12 mg/m^2 by intravenous infusion over a period of 30 to 60 minutes on Day 1 to Day 2.
- Quizartinib: After the end of cytarabine administration, quizartinib will be orally administered at a dose of 20 mg or 40 mg once daily on Day 6 to Day 19.

Consolidation Therapy

- Cytarabine: Cytarabine, which is diluted with 5% glucose solution or 5% normal saline to make a total volume of 300 mL to 500 mL, will be administered at a dose of 3.0 g/m^2 for patients of < 60 years old or 1.5 g/m^2 for patients of ≥ 60 years old (age at the time of registration in the study) by intravenous infusion over a period of 3 hours a total of 6 times every 12 hours on Day 1, Day 3, and Day 5.
- Quizartinib: After the end of the 6th dose of cytarabine, quizartinib will be orally administered at a dose of 20 mg or 40 mg on Day 6 to Day 19.

Figure 5.3-1 Summary of Study Treatment Schedule



<Rationale>

Refer to "1.5 Rationale for the Dosage."

5.3.2 Emergency Procedures and Management in the Event of Quizartinib Overdose

In the event of overdose of quizartinib, the investigator or subinvestigator should immediately assess the patient's condition, and if any symptoms are found, immediately provide appropriate intervention and supportive therapy. The investigator and sponsor will discuss and decide whether the patient may continue study participation or not, taking the status of overdose and the subsequent course of the patient into consideration. For overdose occurring during the DLT assessment period, the patient will be excluded from the DLT assessment (refer to "5.4.4 Enrollment of Additional Patients").

In an overseas Phase 1 study (Study CP0001), quizartinib was tested with treatment cycles of intermittent dosing (14 days on the drug followed by 14 days of rest) at 450 mg/day, and 28-day continuous dosing at 200 and 300 mg/day. No DLTs occurred in 6 patients receiving intermittent dosing at 450 mg/day, whereas Grade 3 QTc

prolongation was seen in 1 of 17 patients on continuous dosing at 200 mg/day and in 3 of 8 patients on continuous dosing at 300 mg/day.

5.3.3 Emergency Procedures and Management in the Event of Cytarabine and Anthracycline Overdoses

In the event of overdose of cytarabine or an anthracycline drug, the investigator or subinvestigator should immediately assess the patient's condition, and if any symptoms are found, immediately provide appropriate intervention and supportive therapy. The investigator and sponsor will discuss and decide whether the patient may continue study participation or not, taking the status of overdose and the subsequent course of the patient into consideration.

5.3.4 Randomization and Blinding

Neither randomization or blinding will be used in the study.

5.4 Assessment of Dose-limiting Toxicity

5.4.1 Definition of Dose-limiting Toxicities

The DLT assessment period is from the start day of quizartinib administration in Cycle 1 of remission induction therapy to the preceding day of Day 1 of Cycle 1 of consolidation therapy (induction phase), and a DLT is defined as any toxicity among AEs that occur during the above period that are assessed to be "related" to quizartinib, as listed below. The severity grade will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Japanese version.

- ≥ Grade 3 non-hematological toxicities (except for the following)
  - Alopecia, anorexia, and fatigue
  - Grade 3 queasy, vomiting, or diarrhea that has improved to ≤ Grade 2 within 7 days after the onset after treatment with antiemetic or antidiarrheal drugs
  - Grade 3 mucositis that has improved to ≤ Grade 2 within 7 days after the onset
  - Grade 3 infections
  - Febrile neutropenia
- Hematological toxicities that have not resolved before Day 1 of Cycle 1 of consolidation therapy, as listed below
  - Peripheral neutropenia (< 500/mm^3)
  - Thrombocytopenia resulting from bone marrow aplasia or hypoplasia (< 20 000/mm^3)

- ≥ Grade 3 thrombocytopenia associated with bleeding (< 50 000/mm^3)
- Grade 4 thrombocytopenia requiring blood transfusion (< 25 000/mm^3)

If there is a day when quizartinib cannot be taken due to any toxicity during the DLT assessment period, the investigator and the sponsor will discuss and decide whether to handle the toxicity as a DLT or not.

5.4.2 Assessment Method of Dose-limiting Toxicity

Quizartinib will be administered at a dose of 20 mg at Level 1 and 40 mg at Level 2. Dose escalation within a single patient is not allowed. For the dose of cytarabine and the anthracycline drug used for remission induction therapy, refer to Section "5.3.1 Dose and Regimen."

DLT assessment at each level will first be conducted in 3 patients (including at least 1 patient of < 60 years old at the time of registration in the study). DLT assessment for each patient will basically be conducted after the end of the DLT assessment period for the patient; however, if both the investigator and the sponsor decide it necessary to terminate the patient's participation in the study, eg, ≥ Grade 3 non-hematological toxicity occurs during the DLT assessment period and is assessed to be "related" to quizartinib, and premature termination of the study is considered necessary to ensure the patient's safety, it is allowed to assess DLTs before the end of the DLT assessment period. If DLTs do not occur in the first 3 patients at Level 1, the treatment will proceed to Level 2. If DLTs occur in the first 3 patients at Level 1, an additional 3 patients will be enrolled at Level 1 or quizartinib dose escalation will be discontinued in accordance with "Table 5.4-1 Criteria for Proceeding to Level 2." If the treatment proceeds to Level 2, the MTD will be determined in accordance with "Table 5.4-2 Criteria for Assessing Maximum Tolerated Doses (MTDs) at Level 2."

Table 5.4-1 Criteria for Proceeding to Level 2

Incidence of DLTs in the first 3 patients at Level 1, and the decision	Incidence of DLTs when 3 patients are additionally enrolled at Level 1 (a total of 6 patients), and the decision
0 of 3 patients: Proceed to Level 2.	—
1 of 3 patients: Additionally enroll 3 patients at Level 1.	1 of 6 patients or 2 of 6 patients: Proceed to Level 2. 3 of 6 patients or 4 of 6 patients: Stop increasing the dose of quizartinib (study termination).
2 of 3 patients or 3 of 3 patients: Stop increasing the dose of quizartinib (study termination).	—

Table 5.4-2 Criteria for Assessing Maximum Tolerated Doses (MTDs) at Level 2

Incidence of DLTs in the first 3 patients at Level 2, and the decision	Incidence of DLTs when 3 patients are additionally enrolled at Level 2 (a total of 6 patients), and the decision
0 of 3 patients: Terminate the study (MTD: 40 mg).	—
1 of 3 patients: Additionally enroll 3 patients at Level 2.	1 of 6 patients or 2 of 6 patients: Terminate the study (MTD: 40 mg). 3 of 6 patients or 4 of 6 patients: Terminate the study (MTD: 20 mg).
2 of 3 patients or 3 of 3 patients: Terminate the study (MTD: 20 mg).	—

If any of the criteria provided in "5.4.4 Enrollment of Additional Patients" is met at Level 1 and any patient is excluded from DLT assessment, information on AEs occurring in the concerned patient, etc. should be taken into consideration to assess whether to proceed to Level 2 or not.

Whether it is necessary or not to establish a new level, in addition to Level 1 and Level 2, will be determined through discussion between the investigator and the sponsor. The medical expert will be consulted as needed.

5.4.3 Determination of Maximum Tolerated Doses

The MTD will be determined in accordance with the assessment criteria given in Table 5.4-2.

5.4.4 Enrollment of Additional Patients

If any of the following apply, the need to enroll additional patients at the level or not will be determined through discussion between the investigator and the sponsor. The medical expert will be consulted as needed. If enrollment of additional patients is determined, the patients meeting any of the following will be excluded from DLT assessment.

- A patient is found to be ineligible after registration.
- A patient has taken quizartinib for the following number of days during the DLT assessment period.
  - The number of days of quizartinib administration is ≤ 9 for patients who have completed remission induction therapy in Cycle 1
  - The number of days of quizartinib administration is ≤ 9 both in Cycle 1 and Cycle 2 for patients who have proceeded to remission induction therapy in Cycle 2.
- A patient takes quizartinib at a higher dose at once than the dose given at the participating level during the DLT assessment period.

- The investigator or the sponsor considers it difficult to assess DLTs in a patient because some procedures during the DLT assessment period have not been performed appropriately.
- A patient is withdrawn from the study because the patient meets the criteria specified in "5.6 Withdrawal Criteria" during the DLT assessment period (except in case the study is terminated due to DLTs).
- Enrollment of additional patients is otherwise considered necessary for safety evaluation.

5.5 Criteria for Temporary Discontinuation, Dose Reduction, and Resumption of Quizartinib

- When the need arises to use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors by necessity during the quizartinib treatment period:
  Quizartinib administration should be temporarily discontinued from the start to the end of use of the above-mentioned drugs. On the day when the quizartinib is resumed after interruption, vital sign measurement, 12-lead ECG, and laboratory tests will be performed before the start of quizartinib administration (refer to "6.2 Remission Induction Therapy" and "6.3 Consolidation Therapy").
- When ≥ Grade 3 QTcF prolongation occurs in a patient at Level 2:
  Quizartinib administration should be temporarily discontinued from the onset time of the above event.
  If the increase in QTcF recovers to ≤ 30 ms, compared with the value at registration, within 14 days after the onset, quizartinib administration will be resumed at a dose reduced to 20 mg/day.
  If the increase in QTcF does not recover to ≤ 30 ms, compared with the value at registration, within 14 days after the onset, the study for the relevant patient will be discontinued.
  * If ≥ Grade 3 QTcF prolongation occurs in a patient at Level 1, the study for the patient should be discontinued (refer to "5.6 Withdrawal Criteria").
- When a DLT occurs (including cases in which it takes time to assess the causality with quizartinib, cytarabine, or the anthracycline drug but the toxicity can potentially be associated with quizartinib):
  If Grade 3 non-hematological toxicity (except QTcF prolongation) occurs during the induction phase and it is assessed to be "related" to quizartinib, quizartinib administration will be temporarily discontinued from the onset time of the event. If

the event resolves to Grade 1 within 28 days after the onset of the event and the investigator or subinvestigator decides it possible to resume quizartinib administration, quizartinib administration will be resumed.
If a Grade 4 non-hematological toxicity (except QTcF prolongation) occurs during the induction phase, the study for the relevant patient will be discontinued.

Once the dose of quizartinib is reduced, the dose should not be increased again to the original dose.

5.6 Withdrawal Criteria

The study treatment must be withdrawn for any of the following reasons:

1) Overt disease progression
2) Intolerable AEs including the following:
   - Grade 4 non-hematological toxicity for which the relationship to the study drug is assessed as "related"
   - (For patients at Level 1) Grade 3 or higher QTcF prolongation or DLT
   - (For patients at Level 2) Any AE that does not lead to a situation allowing the resumption of study treatment, as specified in "5.5 Criteria for Temporary Discontinuation, Dose Reduction, and Resumption of Quizartinib."
3) The need of the second dose reduction in patients with a dose reduction of the study drug
4) Achievement of CR, CRp, or CRi in Cycle 2 or later of consolidation therapy, leading to the decision of the investigator or subinvestigator to introduce HSCT
5) Patient's withdrawal of consent for study participation
6) Ineligibility found after registration in the study
7) Patient found to be pregnant after registration in this study
8) Poor patient compliance with study procedures, including failure to visit the study center as scheduled in the protocol
9) Other circumstances why the study cannot be continued in the investigator's or subinvestigator's opinion

5.7 Prohibited Concomitant Drugs and Therapies, Restricted Concomitant Drugs, and Drugs to Be Coadministered with Care

Prohibited concomitant drugs and therapies:
Concomitant use of the following drugs, etc. is prohibited during the quizartinib

treatment period.
As an exception, the drugs listed in 1) and 2) may be used only when the investigator or subinvestigator considers that these drugs are medically essential to prevent or treat infection. In this case, oral treatment with quizartinib should be interrupted from the start to the end of use of the drugs listed in 1) and 2), and be resumed on the following day of the end of use of the drugs. At the time of resumption, no dose reduction of quizartinib will be necessary unless the investigator or subinvestigator considers it necessary.

1) Drugs that may potentially prolong the QT/QTc interval
2) Strong CYP3A4 inhibitors
3) Strong or moderate CYP3A4 inducers
4) Crude drugs and food products with CYP3A4-inhibiting or -inducing properties (eg, foods and beverages containing St. John's wort or grapefruit)
5) Anticancer treatments other than quizartinib (except hydroxycarbamide)
6) Investigational drugs other than quizartinib, and investigational devices
7) Donor lymphocytes

Restricted concomitant drugs:
The following treatments should be restricted during oral treatment with quizartinib:

- Treatment with hydroxycarbamide for control of the white blood cell count: Restricted to a daily dose of 2 g for up to a total of 14 days

[Drugs to be coadministered with care]
During oral treatment with quizartinib, use of substrates and inhibitors of P-glycoprotein should be avoided as far as possible.

<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 CYP3A4 inhibitors by necessity for the prevention or treatment of infection, concomitant use of these drugs with quizartinib should be avoided.
In addition, in vitro data indicate that quizartinib is a substrate of P-glycoprotein and that it inhibits P-glycoprotein. For this reason, concomitant use of quizartinib with substrates and inhibitors 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. Concomitant use of quizartinib with P-glycoprotein inhibitors may increase the blood concentration of quizartinib and AC886.

5.8 Symptomatic Therapy

No specifications on symptomatic therapy are established in the study.

5.9 Management of Patients

The investigator or subinvestigator will strive to ensure the maximum safety of patients throughout the study period. Patients must be hospitalized during the DLT assessment period (refer to "5.4.1 Definition of Dose-limiting Toxicities"). Patients will be allowed to make a temporary overnight stay outside the hospital during the hospitalization period if the investigator or subinvestigator considers it possible after careful examination of the patient. If a patient makes an overnight stay outside the hospital, the study staff at the study center will instruct the patient how to contact the study center in the event of an emergency, prior to making an overnight stay outside the hospital.
If an AE occurring during hospitalization does not resolve or is not relieved until the planned day of discharge, the investigator or subinvestigator will decide the need to continue hospitalization or not in consideration of patient safety assurance.

6. STUDY PROCEDURES

Study procedures specified in the protocol are shown in "Table 6-1 and Table 6-2 Schedule of Study Procedures."

In the study, the period from the day of informed consent through the end day of post-treatment observation 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
Remission Induction Therapy (Up to 2 Cycles)

				Cycle 1										
		Day of Informed Consent	Day of Registration	Day 1	Day 2	Day 3	Day 7	Day 8	Day 9	Day 11	Day 15	Day 21	Day 22	Day 28
Informed consent		●												
Registration of patients			●											
Administration of the study drug and coadministered drugs*														
7 + 3	Quizartinib							←	—	—	—	→		
	Cytarabine			←	—	—	→							
	Daunorubicin or idarubicin			●	●	●								
5 + 2	Quizartinib							←	—	—	—	→		
	Cytarabine			←	—	—	→							
	Daunorubicin or idarubicin			●	●	●								
Baseline subject characteristics		●												
Medical history/complications		●												
Vital sign measurement**		● ≤ 7 days before registration		●a)				●b)	●		●c)	●b)	●	●e)
Body weight		● ≤ 7 days before registration		●a)				●				●		●e)
ECOG PS assessment		● ≤ 7 days before registration		●a)				●				●		●e)
12-lead ECG**		● ≤ 14 days before registration		●a)				●b)	●		●c)	●b)	●	●e)
Laboratory tests (hematology, blood chemistry, urinalysis)**		● ≤ 14 days before registration		●a)				●			●	●		●e)
Pregnancy test		⊙ ≤ 14 days before registration												
Assessment of bone marrow findings (antitumor effect)		● ≤ 14 days before registration										The day ●		
HIV antibody tests		● ≤ 14 days before registration												
Central measurement	Pharmacokinetics							●d)	●		●c)	●d)	●	●
	FLT3-ITD and c-KIT mutations		●a)											
	Phosphorylated protein levels in blood, including FLT3							●b)	●		●	●		
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein							●b)	●		●	●		
Assessment of concomitant drugs and therapies		←	—	—	—	—	—	—	—	—	—	—	—	—
Monitoring of AEs		←	—	—	—	—	—	—	—	—	—	—	—	—

		Cycle 2										
		Day 1	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 15	Day 19	Day 21	Day 28
Informed consent												
Registration of patients												
Administration of the study drug and coadministered drugs*												
7 + 3	Quizartinib							←	—	—	→	
	Cytarabine	←	—	—	—	—	→					
	Daunorubicin or idarubicin	●	●	●								
5 + 2	Quizartinib					←	—	—	—	→		
	Cytarabine	←	—	—	→							
	Daunorubicin or idarubicin	●	●									
Baseline subject characteristics												
Medical history/complications												
Vital sign measurement**		●a)!				5+2 ●c)		7+3 ●c)	●	5+2 ●	7+3 ●	●e)
Body weight		●a)!										●e)
ECOG PS assessment		●a)!				5+2 ●		7+3 ●		5+2 ●	7+3 ●	●e)
12-lead ECG**		●a)!				5+2 ●c)		7+3 ●c)	●	5+2 ●	7+3 ●	●e)
Laboratory tests (hematology, blood chemistry, urinalysis)**		●a)!				5+2 ●		7+3 ●	●	5+2 ●	7+3 ●	●e)
Pregnancy test												
Assessment of bone marrow findings (antitumor effect)											The day ●	
HIV antibody tests												
Central measurement	Pharmacokinetics											
	FLT3-ITD and c-KIT mutations											
	Phosphorylated protein levels in blood, including FLT3											
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein											
Assessment of concomitant drugs and therapies		→	→	→	→	→	→	→	→	→	→	→
Monitoring of AEs		→	→	→	→	→	→	→	→	→	→	→

● Mandatory, ○ To be performed only in selected patients

a) Before the start of administration of cytarabine and the anthracycline drug
b) Pre-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
c) Pre-dose, 2 hours (±10 minutes) post-dose, and 4 hours (±10 minutes) post-dose
d) Pre-dose, 30 minutes (±10 minutes) post-dose, 1 hour (±10 minutes) post-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
e) −3 days to the day

* Remission induction therapy in Cycle 2 will be given using the same regimen as in Cycle 1 ("7 + 3") or on the dosing schedule ("5 + 2") shown in the table.

** If drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors are used after the start of quizartinib treatment, quizartinib treatment should be interrupted from the start to the end of use of these drugs.
After the day when quizartinib is resumed, the following procedures will be performed at the time points listed below:

[1] Pre-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement, 12-lead ECG, and laboratory tests
[2] 2 hours (±10 minutes) post-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement and 12-lead ECG
[3] Pre-dose of quizartinib on Day 4 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[4] Pre-dose of quizartinib on Day 8 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[5] Pre-dose of quizartinib on Day 11 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[6] Pre-dose of quizartinib on Day 15 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG

! If Cycle 2 is started within +7 days reckoned from Day 28 of Cycle 1, the procedures scheduled on Day 1 of Cycle 2 are not necessary.

Table 6-2 Schedule of Study Procedures

		Cycle 1								
		Before the Start of Treatment	Day 1	Day 3	Day 5	Day 6	Day 7	Day 13	Day 19	Day 21	Day 28
Informed consent		●									
Registration of patients											
Administration of the study drug and coadministered drugs											
	Quizartinib					←	—	—	→		
	Cytarabine		●●	●●	●●						
Baseline subject characteristics											
Medical history/complications											
Vital sign measurement**			●a)			●b)		●c)	●		●d)
Body weight			●a)			●			●		●d)
ECOG PS assessment			●a)			●			●		●d)
12-lead ECG**			●a)			●b)		●c)	●		●d)
Laboratory tests (hematology, blood chemistry, urinalysis)**			●a)			●		●	●		●d)
Pregnancy test		⊙ Within 7 days before treatment									
Assessment of bone marrow findings (antitumor effect)										The day ●	
HIV antibody tests											
Central measurement	Pharmacokinetics					●c)	●	●c)	●		●d)
	FLT3-ITD and c-KIT mutations										
	Phosphorylated protein levels in blood, including FLT3										
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein										
Assessment of concomitant drugs and therapies		←	—	—	—	—	—	—	—	—	→
Monitoring of AEs		←	—	—	—	—	—	—	—	—	→

		Cycle 2 and Thereafter									
		Day 1	Day 3	Day 5	Day 6	Day 13	Day 19	Day 21	Day 28	At Withdrawal	Post-treatment Observation
Informed consent											
Registration of patients											
Administration of the study drug and coadministered drugs											
	Quizartinib				←	—	→				
	Cytarabine	●●	●●	●●							
Baseline subject characteristics											
Medical history/complications											
Vital sign measurement**		●a) !			●	●	●		●d)	●e)	●f)
Body weight		●a) !							●d)	●e)	●f)
ECOG PS assessment		●a) !			●		●		●d)	●e)	●f)
12-lead ECG**		●a) !			●	●	●		●d)	●e)	●f)
Laboratory tests (hematology, blood chemistry, urinalysis)**		●a) !			●	●	●		●d)	●e)	●f)
Pregnancy test											
Assessment of bone marrow findings (antitumor effect)								The day ●		●e)	
HIV antibody tests											
Central measurement	Pharmacokinetics										
	FLT3-ITD and c-KIT mutations										
	Phosphorylated protein levels in blood, including FLT3										
	Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein										
Assessment of concomitant drugs and therapies		→									
Monitoring of AEs		→									

● Mandatory, ○ To be performed only in selected patients

a) Before the start of cytarabine administration
b) Pre-dose, 2 hours (±10 minutes) post-dose, 4 hours (±10 minutes) post-dose, and 6 hours (±10 minutes) post-dose
c) Pre-dose, 2 hours (±10 minutes) post-dose, and 4 hours (±10 minutes) post-dose
d) −3 days to the day
e) Day when study termination is decided (−3 days to +7 days)
f) 28th day (±7 days) reckoned from the day of the last dose of the study drug

** If drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors are used after the start of quizartinib treatment, quizartinib treatment should be interrupted from the start to the end of use of these drugs.
After the day when quizartinib is resumed, the following procedures will be performed at the time points listed below:

[1] Pre-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement, 12-lead ECG, and laboratory tests
[2] 2 hours (±10 minutes) post-dose of quizartinib on the day when the drug is resumed:	Vital sign measurement and 12-lead ECG
[3] Pre-dose of quizartinib on Day 4 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[4] Pre-dose of quizartinib on Day 8 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[5] Pre-dose of quizartinib on Day 11 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG
[6] Pre-dose of quizartinib on Day 15 (±1 day) when defining the day when the drug is resumed as Day 1:	Vital sign measurement and 12-lead ECG

! If the next cycle is started within +7 days reckoned from Day 28 of each cycle, the procedures scheduled on Day 1 of the next cycle are not necessary.

6.1 Informed Consent to 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.

1) Items to be collected or assessed after informed consent is obtained but before the start of the patient registration procedure
   - Date of informed consent for participation in the study
   - Subject identification code
   - Date of birth
   - Sex
   - Race
   - Height
   - Eligibility
   - Medical history and complications:
     Assess the presence or absence of medical history and complications, the presence or absence of symptoms at the time of informed consent (if any symptoms are present, it should be handled as a complication), findings, and the diagnosis.
     Regarding medical history, record only the symptoms/diseases that have been cured by the time of informed consent and are considered necessary to be reported in the investigator's or subinvestigator's opinion.
   - Information on the underlying disease (AML):
     The date when the patient was diagnosed with AML and WHO classification will be confirmed.
   - AEs
     The occurrence of AEs after the day of informed consent will be monitored according to "9. SAFETY ENDPOINTS."
   - Concomitant drugs and therapies
     Collect data on the following items concerning drugs and therapies used after the day of informed consent:
     - 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 transfusions performed after the day of informed consent will be confirmed.

  Type of blood products (whole blood, red blood cells, plasma, platelets, others), start date, end date, amount of use (unit), and reason for use

2) Items to be collected or assessed between Day −7 and Day 0 (= day of registration)
   - Vital sign measurement

     Axillary body temperature, pulse rate, systolic blood pressure, and diastolic blood pressure will be measured in the resting state.
   - Body weight
   - ECOG PS assessment

     “Appendix 1 ECOG Performance Status (PS)” should be followed for assessment.

3) 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)
   - 12-lead ECG (including QTcF assessment)

     ECG will be performed in patients after a 10-minute rest in the supine position. For QTcF assessment, triplicate ECG recordings will be obtained at about 2-minute intervals. If 12-lead ECG and blood collection for laboratory tests, etc. are conducted on the same day, the 12-lead ECG will be followed by blood collection.

- Laboratory tests

	Laboratory Parameter
Hematology test	Red blood cell count, reticulocyte, 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, prothrombin time (PT), and prothrombin time-international normalized ratio (PT-INR)
Blood chemistry test	Total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, ALP, γ-GT, LDH, lipase, BUN, serum creatinine, creatine kinase, uric acid, glucose, bicarbonate, electrolytes (K, Na, Cl, Ca, P, Mg), and CRP
Urinalysis	Appearance, color, specific gravity, pH, occult blood, glucose, protein, bilirubin, and ketone bodies

- Assessment of bone marrow findings

  Bone marrow findings and neutrophil and platelet counts in the peripheral blood will be assessed as specified in "10.1 Definition of Efficacy Endpoints."
- 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 12 months 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 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.
- HIV antibody

6.2 Remission Induction Therapy

Remission induction therapy will be given for up to 2 cycles, each of which is 28 days long.

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 specified in "6.1 Informed Consent to Patient Registration."

Bone marrow aspiration or biopsy will be performed on Day 21 of Cycle 1; if myeloblasts account for < 5%, the treatment will proceed to Cycle 1 of consolidation therapy (Cycle 2 of remission induction therapy will be skipped); if myeloblasts account for ≥ 5%, remission induction therapy in Cycle 2 will be given.

The start of Cycle 2 can be postponed within a range of +56 days from Day 1 of Cycle 1.

If Cycle 2 is started within +7 days reckoned from Day 28 of Cycle 1, the procedures (vital signs measurement, body weight measurement, ECOG PS assessment, 12-lead ECG measurement, and laboratory tests) scheduled on Day 1 of Cycle 2 are not necessary.

1) Confirmation of the status of administration of the study drug and coadministered drugs (cytarabine and the anthracycline drug)
   - Prescribed doses administered or not administered
   - Dates of doses administered
   - Timing of dosing
   - Amount of dose administered
   - Presence or absence of temporary discontinuation and dose reduction (if present, the details and reason for it)

   Patients are instructed to record the presence or absence of quizartinib administration, and the time of administration, etc. in the dosing diary. The investigator or subinvestigator will check the status of quizartinib administration based on the information in the dosing diary.

2) Vital sign measurement

Cycle 1	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 9	Before administration of quizartinib
	Day 15	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 22	—
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "7 + 3"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 15	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "5 + 2"	Day 1	Before the start of administration of cytarabine and the anthracycline drug

	Day 6 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 15	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, vital signs will be measured at the following time points: [1] pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the day when quizartinib is resumed); [2] 2 hours (±10 minutes) post-dose on the day when quizartinib is resumed; [3] pre-dose on Day 4 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [4] pre-dose on Day 8 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [5] pre-dose on Day 11 (±1 day) if the day when quizartinib is resumed is defined as Day 1; and [6] pre-dose on Day 15 (±1 day) if the day when quizartinib is resumed is defined as Day 1.

3) Body weight

Cycle 1	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "7 + 3"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "5 + 2"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 28 (−3 days to the day)	—

4) ECOG PS assessment

Cycle 1	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "7 + 3"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib
	Day 21	Before administration of quizartinib

	* Last day of quizartinib administration	
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "5 + 2"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

5) 12-lead ECG

If 12-lead ECG and blood collection for laboratory tests, etc. are scheduled at the same time, the 12-lead ECG will be followed by blood collection.

Cycle 1	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 9	Before administration of quizartinib
	Day 15	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 22	—
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "7 + 3"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 15	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "5 + 2"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 6 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 15	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, 12-lead ECG will be measured at the following time points: [1] pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the

day when quizartinib is resumed); [2] 2 hours (±10 minutes) post-dose on the day when quizartinib is resumed; [3] pre-dose on Day 4 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [4] pre-dose on Day 8 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [5] pre-dose on Day 11 (±1 day) if the day when quizartinib is resumed is defined as Day 1; and [6] pre-dose on Day 15 (±1 day) if the day when quizartinib is resumed is defined as Day 1.

6) Laboratory tests

Cycle 1	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib
	Day 15	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "7 + 3"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 8 * First day of quizartinib administration	Before administration of quizartinib
	Day 15	Before administration of quizartinib
	Day 21 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 * In case of "5 + 2"	Day 1	Before the start of administration of cytarabine and the anthracycline drug
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 15	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, laboratory tests will be performed pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the day when quizartinib is resumed).

7) Assessment of antitumor effect

Bone marrow findings and neutrophil and platelet counts in the peripheral blood will be assessed as specified in "10.1 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 1	Day 21	On the specified day
Cycle 2 * In case of "7 + 3"	Day 21	On the specified day
Cycle 2 * In case of "5 + 2"	Day 21	On the specified day

8) Monitoring of AEs

9) Assessment of concomitant drugs and therapies

10) Collection of specimens for pharmacokinetic assessment and the biomarker study
Refer to "6.7 Pharmacokinetics" and "6.8 Biomarker Study."

6.3 Consolidation Therapy

Remission induction therapy will be given for up to 4 cycles, each of which is 28 days long.

The start of Cycle 2 and subsequent cycles can be postponed within a range of +56 days from Day 1 of the preceding cycle if the investigator or subinvestigator considers it necessary. Patients who have achieved CR, CRp, or CRi in Cycle 2 or later are allowed to terminate consolidation therapy and undergo HSCT. In such a case, however, the study treatment for the relevant patient should be discontinued (refer to "5.6 Withdrawal Criteria").

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 specified in "6.1 Informed Consent to Patient Registration."

If the next cycle is started within +7 days reckoned from Day 28 of each cycle, the procedures (vital signs measurement, body weight measurement, ECOG PS assessment, 12-lead ECG measurement, and laboratory tests) scheduled on Day 1 of the next cycle are not necessary.

1) Confirmation of the status of administration of the study drug and coadministered drugs (cytarabine and the anthracycline drug)
   - Prescribed doses administered or not administered
   - Dates of doses administered

- Timing of dosing
- Amount of dose administered
- Presence or absence of temporary discontinuation and dose reduction (if present, the details and reason for it)

Patients are instructed to record the presence or absence of quizartinib administration, and the time of administration, etc. in the dosing diary. The investigator or subinvestigator will check the status of quizartinib administration based on the information in the dosing diary.

2) Vital sign measurement

Cycle 1	Day 1	Before the start of cytarabine administration
	Day 6 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 13	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 and thereafter	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 13	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, vital signs will be measured at the following time points: [1] pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the day when quizartinib is resumed); [2] 2 hours (±10 minutes) post-dose on the day when quizartinib is resumed; [3] pre-dose on Day 4 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [4] pre-dose on Day 8 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [5] pre-dose on Day 11 (±1 day) if the day when quizartinib is resumed is defined as Day 1; and [6] pre-dose on Day 15 (±1 day) if the day when quizartinib is resumed is defined as Day 1.

3) Body weight

Cycle 1	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 and thereafter	Day 1	Before the start of administration of cytarabine
	Day 28 (−3 days to the day)	—

4) ECOG PS assessment

Cycle 1	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 and thereafter	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

5) 12-lead ECG

If 12-lead ECG and blood collection for laboratory tests, etc. are scheduled at the same time, the 12-lead ECG will be followed by blood collection.

Cycle 1	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 13	Before administration of quizartinib 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 and thereafter	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 13	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, 12-lead ECG will be measured at the following time points: [1] pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the day when quizartinib is resumed); [2] 2 hours (±10 minutes) post-dose on the day when quizartinib is resumed; [3] pre-dose on Day 4 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [4] pre-dose on Day 8 (±1 day) if the day when quizartinib is resumed is defined as Day 1; [5] pre-dose on Day 11 (±1 day) if the day when quizartinib is resumed is defined as Day 1; and [6] pre-dose on Day 15 (±1 day) if the day when quizartinib is resumed is defined as Day 1.

6) Laboratory tests

Cycle 1	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 13	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—
Cycle 2 and thereafter	Day 1	Before the start of administration of cytarabine
	Day 6 * First day of quizartinib administration	Before administration of quizartinib
	Day 13	Before administration of quizartinib
	Day 19 * Last day of quizartinib administration	Before administration of quizartinib
	Day 28 (−3 days to the day)	—

In patients who use drugs that may potentially prolong the QT/QTc interval or strong CYP3A4 inhibitors, laboratory tests will be performed pre-dose of quizartinib on the following day of the end of use of the drugs (ie, the day when quizartinib is resumed).

7) Pregnancy test

Patients who have undergone a pregnancy test (urine or serum test) before registration in the study are required to undergo a pregnancy test again before the start of treatment with coadministered drugs on Day 1 of Cycle 1 (−7 days to the day). If the result is positive, the study for the relevant patient will be discontinued (refer to “5.6 Withdrawal Criteria”).

8) Assessment of antitumor effect

Bone marrow findings and neutrophil and platelet counts in the peripheral blood will

be assessed as specified in "10.1 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 1	Day 21	On the specified day
Cycle 2 and thereafter	Day 21	On the specified day

9) Monitoring of AEs

10) Assessment of concomitant drugs and therapies

11) Collection of specimens for pharmacokinetic assessment and the biomarker study
Refer to "6.7 Pharmacokinetics" and "6.8 Biomarker Study."

6.4 At the Time of Withdrawal from the Study

The procedures listed below will be performed within the day of the investigator's or subinvestigator's decision to withdraw a patient from the study (−3 days to +7 days). The details of the procedures are the same as those specified in "6.1 Informed Consent to Patient Registration."

- Date of and reason for withdrawal
- Vital sign measurement
- Body weight
- ECOG PS assessment
- 12-lead ECG
- Laboratory tests
- Assessment of antitumor effect
- Monitoring of AEs
- Assessment of concomitant drugs and therapies

6.5 Post-treatment Observation Period

The procedures listed below will be performed at 28 days (±7 days) reckoned from the day of the last dose of the study drug. If any AE has not resolved at the time point when the procedures are performed, follow-up should be continued as far as possible until the AE is confirmed to have resolved or be resolving.

- Confirmation of survival or death (The "date of final confirmation" when the patient

is alive and the "date of death" when the patient is dead will be recorded in the CRF.)

- Vital sign measurement
- Body weight
- ECOG PS assessment
- 12-lead ECG
- Laboratory tests
- Monitoring of AEs
- Assessment of concomitant drugs and therapies (Concomitant drugs and therapies used for AEs, if any, will be recorded in the CRF.)
- Confirmation of the presence or absence of post treatment (If treatment meeting the definition specified in "6.6 Post Treatment" is started after the following day of the last dose of the study drug, the treatment regimen and the start date will be recorded in the CRF.)

6.6 Post Treatment

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

6.7 Pharmacokinetics

After 2 mL of blood is collected from each patient, as specified in "Table 6.7-1 Blood Collection Points for Pharmacokinetic Assessment," the plasma specimens will immediately be stored in a frozen state at −90°C to −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.

Table 6.7-1 Blood Collection Points for Pharmacokinetic Assessment

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Limit)
Remission induction therapy Cycle 1	Day 8 * First day of quizartinib administration	Pre-dose 30 minutes (±10 minutes) post-dose 1 hour (±10 minutes) post-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 9	Pre-dose
	Day 15	Pre-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose

	Day 21 * Last day of quizartinib administration	Pre-dose 30 minutes (±10 minutes) post-dose 1 hour (±10 minutes) post-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 22	On the specified day
	Day 28	On the specified day
Consolidation therapy Cycle 1	Day 6 * First day of quizartinib administration	Pre-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 7	Pre-dose
	Day 13	Pre-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose
	Day 19 * Last day of quizartinib administration	Pre-dose
	Day 28 (−3 days to the day)	On the specified day

6.8 Biomarker Study

Quizartinib-related biomarkers and biomarkers that allow the prediction of efficacy and others of quizartinib will be explored. Details including the handling of specimens for each study item will be specified in separate procedures. The date and time of specimen collection will be recorded in the CRF.

6.8.1 FLT3-ITD Status and c-KIT Mutations

The following specimens will be collected before the start of administration of coadministered drugs (cytarabine and the anthracycline drug): 1 mL of bone marrow liquid or 2 mL of peripheral blood for analysis of the FLT3-ITD status, and 1 mL of bone marrow liquid or 7 mL of peripheral blood for analysis of c-KIT mutations. The specimens under refrigeration will be submitted to the agency contracted by the sponsor to collect the specimens.

6.8.2 Phosphorylated FLT3, STAT5, and c-KIT Protein Levels in Blood

After 2 mL of blood is collected from each patient as specified in "Table 6.8-1 Blood Collection Points (Phosphorylated Protein Levels in Blood)," the plasma specimens will immediately be stored in a frozen state at −90°C to −70°C. The specimens in a frozen state will be submitted to the agency contracted by the sponsor to collect the specimens.

Table 6.8-1 Blood Collection Points (Phosphorylated Protein Levels in Blood)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Limit)
Remission induction therapy Cycle 1	Day 8 * First day of quizartinib administration	Pre-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 9	Pre-dose
	Day 15	Pre-dose
	Day 21 * Last day of quizartinib administration	Pre-dose

6.8.3 Inhibitory Activity of Plasma Quizartinib on Phosphorylated FLT3 Protein

After 5 mL of blood is collected from each patient as specified in "Table 6.8-2 Blood Collection Points (Inhibitory Activity of Plasma Quizartinib on Phosphorylated FLT3 Protein)," the specimens will be prepared and immediately be stored in a frozen state at −90°C to −70°C. The specimens in a frozen state will be submitted to the agency contracted by the sponsor to collect the specimens.

Table 6.8-2 Blood Collection Points (Inhibitory Activity of Plasma Quizartinib on Phosphorylated FLT3 Protein)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Limit)
Remission induction therapy Cycle 1	Day 8 * First day of quizartinib administration	Pre-dose 2 hours (±10 minutes) post-dose 4 hours (±10 minutes) post-dose 6 hours (±10 minutes) post-dose
	Day 9	Pre-dose
	Day 15	Pre-dose
	Day 21 * Last day of quizartinib administration	Pre-dose

6.9 Anonymization, Storage, and Disposal of Specimens for the Biomarker Study

6.9.1 Anonymization of Specimens

The specimens will be anonymized by each of the study centers and the specimen collection agency according to the procedure described below.

The study center will never provide information that can identify individual patients to the specimen collection agency. The anonymity numbers will be strictly stored by the specimen storage manager at the specimen collection agency and will not be provided to the study center.

1) The study center will assign a "subject identification code" to each patient. The correspondence table between the "medical record number" and the "subject identification code" that can identify personal information will be stored at the study

center.

2) The specimen collection agency will assign an "anonymity number" to the collected specimens of each patient and attach a label displaying the "anonymity number," in place of the "subject identification code," to each specimen. The correspondence table between "subject identification code" and "anonymity number" will be prepared by the specimen collection agency and be stored by the sponsor.

6.9.2 Storage and Disposal of Specimens

The sponsor will be responsible for disposal of the specimens as requested by patients via the investigator and disposal after the end of the storage period. Specimens will be stored for a maximum of up to 3 years after completion of the study.

At the expiration of the storage period, the specimen collection agency and the central laboratory will dispose of the specimens according to the sponsor's directions. For specimens that the sponsor considers are not necessary to be stored any longer, even during the specimen storage period, the specimen collection agency and the central laboratories will dispose of the specimens according to the sponsor's directions.

If a patient withdraws consent for the study and requests the study center to dispose of the biomarker specimens during the specimen storage period, the specimens will be disposed of, depending on the location of the specimens at the time of the request, according to the following procedure:

1) In cases where the specimens are temporarily stored at the study center:
   The investigator or subinvestigator 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 central laboratory:
   The investigator or subinvestigator will report the subject identification code of the pertinent patient to the sponsor. The sponsor will identify the specimens of the patient based on the correspondence table linking the subject identification code with the anonymity number, inform the specimen collection agency or the central laboratory of the anonymity number, and direct the agency or laboratory to dispose of the specimens. The specimen collection agency or the central laboratory will dispose of the specimens according to the sponsor's directions.

Specimens collected for the assessment of FLT3-ITD status and c-KIT mutations of a patient who withdraws consent should be disposed of promptly in accordance with the Ethical Guidelines for Human Genome/Gene Analysis Research.[18)] Regarding the other

specimens of the patient, the sponsor will decide on the timing of disposal.
Specimens of a patient who withdraws consent should be managed strictly by separating them from the specimens of other patients until they are disposed of. The sponsor is responsible for the management of the specimens.

7. PHARMACOKINETIC ENDPOINTS

The following pharmacokinetic parameters will be calculated by a non-compartment model approach using plasma concentration data of quizartinib and its active metabolite AC886 obtained on Day 8 of Cycle 1 and Day 21 of Cycle 1 during the induction phase.

Day 8 of Cycle 1 during the induction phase: Cmax, Tmax, AUCtau

Day 21 of Cycle 1 during the induction phase: 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. PHARMACODYNAMIC ENDPOINTS

The following endpoints will be measured:

- FLT3-ITD status and c-KIT mutations (bone marrow liquid or blood specimens)
- Phosphorylated FLT3, STAT5, and c-KIT protein levels in blood (blood specimens)
- Inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein (plasma specimens)

9. SAFETY ENDPOINTS

Safety endpoints are defined as AEs, laboratory data, body weight, vital signs, and 12-lead ECG.

9.1 Definition of Adverse Events

An AE is any untoward or unintended sign (including an abnormal change in laboratory findings or vital signs), symptom, or disease noted between the day of informed consent for the study and the end day of post-treatment observation, whether it is considered to be related to the study drug or not.

A symptom or disease preexisting before informed consent for the study is obtained will be handled as a complication, not as an AE. Any complication that is exacerbated after informed consent for the study is obtained should be handled as an AE, and the date when the exacerbation is detected will be recorded as the date of onset of the AE.

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

- Tumor progression will not be handled as an AE, in principle. 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.

9.2 Definition of Serious Adverse Events

An SAE is any AE that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization for treatment,
- is a disability or incapacity,
- may lead to a disability or incapacity,
- represents other medically important condition, or
- is a congenital anomaly or birth defect.

9.3 Adverse Event Information to Be Reported

If an AE occurs during the study, the items shown in “Table 9.3-1 Investigation Items following Onset of Adverse Events” will be investigated and recorded in the CRF, etc.

Only the highest grade observed in the course of each AE should be recorded as the severity in the CRF.

Table 9.3-1 Investigation Items following Onset of Adverse Events

Item		Details to Be Investigated	
AE		Name of AE, date of onset	
Intervention for AE		Presence or absence of intervention (including changes in study drug administration), and if present, the content of the intervention	
Outcome		Outcome category, date of outcome assessment, date of resolution	
	Outcome category	Recovered/ Resolved	The AE has resolved, and the patient has recovered to the pre-event condition.
		Recovering/ Resolving	The AE has almost resolved, and the patient has nearly recovered to the pre-event condition.
		Not recovered/ Not resolved	The AE has not resolved, and the condition of the patient is similar to that at onset (unchanged).
		Recovered/ Resolved with sequelae/residual effect(s) present	The AE has resolved, but the patient has sequelae.
		Fatal	The event outcome is fatal only when the investigator considers that the AE and the patient's death are related or that a relationship cannot be ruled out. Death due to worsening of the underlying disease is not applicable to this category.
		Unknown	Outcome is unknown because of lack of information.
Severity		To be assessed according to the CTCAE v4.0 Japanese version. The severity of AEs not included in the CTCAE v4.0 Japanese version will be assessed according to the following grades:	
		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 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.
Seriousness		Serious/Nonserious	
Causality with the study drug and coadministered drugs (cytarabine and the anthracycline drug)		Classification of the relationship (in accordance with the following classification of the relationship)	
	Causality category	Related	• There is a reasonable temporal relationship between the onset of the AE and administration of the study drug, it is not reasonable to assess that the AE is attributable to the patient's condition or other factors than the study drug (underlying disease, complications, concomitant drugs, etc.), and a relationship with the study drug cannot be ruled out. • There is a reasonable temporal relationship between the onset of the AE and administration of the study drug, and the AE can be explained by known actions or the pharmacological action of the study drug or similar analogues.
		Unrelated	• There is no reasonable temporal relationship between the onset of the AE and administration of the study drug, it is reasonable to assess that the AE is attributable to the patient's condition or other factors than the study drug (underlying disease, complications, concomitant drugs), and a relationship with the study drug can be ruled out.

9.4 Definition of Adverse Drug Reactions

AEs that are assessed as "related" to the study drug will be handled as adverse drug reactions.

9.5 Actions to Be Taken for Adverse Events

9.5.1 Recommended Action for Adverse Events

If any AE has occurred, the investigator or subinvestigator 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 this study. 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 investigator or subinvestigator 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).

9.5.2 Action for Serious Adverse Events

If an SAE has occurred, the investigator or subinvestigator will take appropriate actions, and report the details of the SAE to the sponsor by telephone or fax within 24 hours of learning of the occurrence. The investigator will subsequently enter the necessary information in the Serious Adverse Event Report (SAVER) FORM (Appendix 3) and submit the form with the date of confirmation and a signature to the sponsor without delay. 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.

9.6 Actions to Be Taken in the Event That Information on Pregnancy, Pregnant and Parturient Women, and Delivery Is Obtained

If information on the pregnancy of a patient or a patient's female partner is obtained during the study period or within 6 months after the last dose of the study drug, the investigator or subinvestigator will investigate the information on the pregnancy through delivery, and report it to the sponsor using the format provided by the sponsor (Appendix 4). Pregnancy will not be handled as an AE; however, if the outcome of the pregnant woman falls under the definition of SAEs (congenital anomaly in the fetus [including suspected cases], stillbirth, and abortion), the investigator or subinvestigator must report it to the sponsor in accordance with the procedures for reporting SAEs specified in "9.5.2 Action for Serious Adverse Events," independent of whether it is during the study period or not.

10. EFFICACY ENDPOINTS

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 "10.1 Definition of Efficacy Endpoints."

10.1 Definition of Efficacy Endpoints

The efficacy endpoints are defined as follows:

Table 10.1-1 Definition of Efficacy Endpoints

Complete remission (CR)	For patients to be classified as CR, they must achieve a morphologic leukemia-free state, must have < 5% bone marrow blasts in the bone marrow, a neutrophil count ≥ 1000 /mm^3, and a platelet count ≥ 100 000 /mm^3, must be independent of 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 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).
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 < 1000 /mm^3. Platelet recovery status and RBC and platelet transfusion independence are not required.
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.
No response (NR)	NR is defined as a condition not reaching any of CR, CRp, CRi, or PR.
Composite CR rate (CRc rate)	Composite CR rate (CRc rate) is defined as the proportion of patients whose best response is any of CR, CRp, and CRi.
Response rate	Response rate is defined as the proportion of patients whose best response is any of CR, CRp, CRi, and PR.
Relapse	Relapse after CR, CRp, or CRi: 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 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 > 25%, or the reappearance or new appearance of extramedullary leukemia.

10.2 Best Response

Best response is defined as the best measured response (CR, CRp, CRi, PR, or NR) over all response assessments at all time points after the start of study treatment.

11. STATISTICAL ANALYSES

An outline of the statistical and pharmacokinetic analyses is provided below. Details will be specified in the Statistical Analysis Plan.

11.1 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 and be assessed individually. Patients with a quizartinib dose reduction for any reason after the start of study treatment will be analyzed as patients at the dosing level at the start of study treatment.
The sponsor will also finalize the population flag of patients who are not specified in the protocol or the Statistical Analysis Plan based on the advice of the medical expert as needed.

11.1.1 Safety Analysis Set

The Safety Analysis Set is defined as patients who received at least 1 dose of any of the study drug, cytarabine, and the anthracycline drug.

11.1.2 Efficacy Analysis Set

The Efficacy Analysis Set is defined as patients who received at least 1 dose of the study drug and who have available data of the antitumor effect assessed at least at 1 time point after the start of study treatment.

11.1.3 MTD Analysis Set

The MTD Analysis Set is defined as patients who received at least 1 dose of any of the study drug, cytarabine, and the anthracycline drug, but excludes the patients listed below.

- Patients whose DLT assessment has not been performed appropriately because some of the procedures during the DLT assessment period are missing for other reasons than adverse drug reactions (eg, worsening of the clinical condition due to progression of the primary disease, AEs that are assessed as not related to the study drug)
- Patients who have taken quizartinib for the following number of days during the DLT assessment period
    - The number of days of quizartinib administration is ≤ 9 for patients who have

completed remission induction therapy in Cycle 1

- The number of days of quizartinib administration is ≤ 9 both in Cycle 1 and Cycle 2 for patients who have proceeded to remission induction therapy in Cycle 2.

11.1.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is defined as patients who received at least 1 dose of the study drug, who provided specimens for pharmacokinetic assessment, and who have available measurement data obtained with the specimens.

11.1.5 Pharmacodynamic (Biomarker) Analysis Set

The Pharmacodynamic (Biomarker) Analysis Set is defined as patients who received at least 1 dose of the study drug, who provided specimens for the biomarker study, and who have available data on FLT3-ITD status obtained with the specimens.

11.2 Data Handling

The sponsor will decide the handling of individual data in consultation with the medical expert and lock data.

11.3 Statistical Analysis Items and Methods

11.3.1 Baseline Subject Characteristics

To analyze baseline subject characteristics (demographic variables and other baseline characteristics), frequency tables will be prepared for categorical data and summary statistics will be calculated for quantitative data. Analyses will be performed on the Safety Analysis Set, Efficacy Analysis Set, MTD Analysis Set, Pharmacokinetic Analysis Set, and Pharmacodynamic (Biomarker) Analysis Set.

11.3.2 Safety Analysis

Other safety analyses than DLT analyses will be performed on the Safety Analysis Set, whereas DLT analyses will be performed on the MTD Analysis Set.
AEs that occur or worsen relative to the pre-treatment state after the start of study treatment (treatment emergent AEs [TEAEs]) will be tabulated. AEs collected in the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and be

tabulated by body organ group using the MedDRA system organ class (SOC) and by AE term using preferred terms (PT).

11.3.2.1 Adverse Events

For all TEAEs and TEAEs assessed as "related" to the study drug or a coadministered drug (cytarabine or the anthracycline drug), frequency tables will be prepared for patients with TEAEs as classified below.

The grade of each AE will be assessed according to the CTCAE v4.0 Japanese version.

- TEAEs (by grade; including classification into ≥ Grade 3 events and others)
- Serious TEAEs
- Patients who have postponed administration of the study drug due to TEAEs
- Patients who have postponed administration of a coadministered drug (cytarabine or the anthracycline drug) due to TEAEs
- Patients with treatment discontinuation because of TEAE

11.3.2.2 Individual Adverse Events

For all TEAEs and TEAEs assessed as "related" to the study drug or a coadministered drug (cytarabine or the anthracycline drug), frequency tables will be prepared according to the following categories. If a patient reports the same event several times, only the highest-grade event will be counted for tabulation by grade.

- TEAEs
- TEAEs by grade (including classification into ≤ Grade 2 events and ≥ Grade 3 events)
- TEAEs leading to postponement of administration of the study drug
- TEAEs leading to postponement of administration of a coadministered drug (cytarabine or the anthracycline drug)
- TEAEs causing treatment discontinuation

11.3.2.3 Dose-limiting Toxicity

DLTs will be summarized by frequency tables.

11.3.2.4 Laboratory Data

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.

11.3.2.5 Vital Signs and Body Weight

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.

11.3.2.6 12-lead Electrocardiogram

For 12-lead ECG findings, shift tables of normal-abnormal assessments before the first dose of the study drug and at each time point will be prepared. For PR, QRS, RR, QT, 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 be prepared according to the following categories.

Increase in 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 Efficacy Analysis

In the Efficacy Analysis Set, frequency tables will be prepared for CR, CRp, CRi, PR, and NR at each time point as well as for best response. The CRc rate (CR + CRp + CRi), response rate (CRc + PR), and their 95% confidence intervals will be calculated.

11.3.4 Pharmacokinetic Analysis

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 also be calculated.

11.3.5 Pharmacodynamic (Biomarker) Analysis

In the Pharmacodynamic (Biomarker) Analysis Set, frequency tables will be prepared for

the FLT3-ITD status and the c-KIT mutation status. For phosphorylated FLT3, STAT5, and c-KIT protein levels in blood and the inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein, the measured values will be summarized at each time point.

11.4 Changes to the Analysis Plan

If it is considered necessary to change the planned analyses, the sponsor will examine the appropriateness of the change and potential effects on the study results, and determine whether to make the change or not. The sponsor will clearly document and retain the content of examination of the change in the planned analyses, the presence or absence of the change, and if the change is made, the reason. If a change in the planned analyses is made, the details of and the reason for the change will be documented in the clinical study report.

11.5 Planned Sample Size

Six to twelve patients (minimum of 3 patients at each level, a total of 6 patients)

<Rationale>

The sample size was set as a minimum of 3 patients at each level and it was planned to additionally enroll up to 6 patients based on the status of occurrence of DLTs in reference to the Guidelines for the Clinical Evaluation of Anticancer Drugs.[17)]

12. 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.

13. PAYMENT FOR PARTICIPATION, COMPENSATION FOR STUDY-RELATED INJURIES, AND INSURANCE

13.1 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.

13.2 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. In the event of any study-related injury occurring in a subject, 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. For injuries that are as severe as requiring hospitalization, the sponsor will also pay a medical allowance based on the amount set in 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.

13.3 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.

14. PUBLICATION POLICY

1) 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.
2) 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 5 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. STUDY ADMINISTRATIVE INFORMATION

15.1 Ethics

15.1.1 Ethical Conduct of the Study

This study will be conducted in compliance with the standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the PMD Act and the "Ordinance on Good Clinical Practice" (MHW Ordinance No. 28, dated 27 Mar 1997) (hereinafter, the GCP ordinance). It will also be conducted in compliance with the ethical principles of the Declaration of Helsinki to ensure that the human rights, wellbeing, and safety of subjects are protected to the maximum extent.

The genome/gene analysis to be performed during the study will be performed in accordance with the "Ethical Guidelines for Human Genome/Gene Analysis Research[18)]" and the "Ethical Guidelines for Clinical Studies[19)]" in addition to the above-mentioned regulations.

15.1.2 Institutional Review Board

Prior to the start of the study, it must be reviewed and approved by the Institutional Review Board (IRB) specified in Section 27 of the GCP ordinance. During the course of the study, the appropriateness of study continuation will be reviewed annually, or more frequently upon the IRB's request. The appropriateness of study continuation will also be reviewed if any information that may affect the safety of subjects or the conduct of the study is obtained.

15.2 Subject Confidentiality

To protect the privacy of individual subjects, the subject identification code and subject number, rather than the name or medical chart number that may lead to personal identification, will be used to identify subjects in the documents submitted outside the study center. Any personal information obtained in the course of the study will be kept confidential.

15.3 Procedures for Informed Consent

The investigator or subinvestigator will explain the details of the study listed below to subject candidates in a readily understandable way using the informed consent documents, before any invasive procedures related to the study are performed in each subject, and obtain written informed consent to participate in the study by their free will. Before obtaining consent, the investigator or subinvestigator should give the subject

candidates ample time and opportunity to ask questions to decide whether to participate in the study, and should answer the questions in an appropriate manner.
Before the start of study drug administration in Cycle 1 of consolidation therapy, written informed consent to continue participation in the study after the end of the DLT assessment period will be obtained again from the subjects. For subjects who experienced any DLTs during the DLT assessment period, written informed consent to continue participation in the study will be obtained again before resuming the study drug administration after recovery from the toxicity.
The investigator or subinvestigator who has provided an explanation and the subject who has given consent will sign and date the consent form. If study staff personnel provide a supplementary explanation to the subject candidates, the study staff should sign and date the form. The investigator or subinvestigator will provide a copy of the consent form along with the subject information form to the subject, and retain the original consent form at the study center. The investigator or subinvestigator will document (eg, in the original consent form or medical record) that a copy of the consent form and subject information form have been provided to the subject.

[Items to be explained to the subjects]

1) That the study involves research
2) Study objectives
3) Study methods (including the research aspects of the study and the inclusion and exclusion criteria of the study)
4) The expected duration of each subject's participation in the study
5) Planned number of subjects in the study
6) Foreseeable physical and mental benefits and risks associated with the study drug
7) Presence or absence of other treatment methods and expected important benefits and risks of the methods
8) Compensation and treatment that the subject can receive if any study-related injury occurs as a result of participation in the study
9) Statements that participation in the study is based on the subject's own free will; that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she refuses to participate in or withdraw from the study; and that he/she will not lose any benefits that would have been given, even if he/she does not participate in the study
10) A statement that the subject will be promptly informed if any information that may affect his/her willingness to continue participation in the study is obtained

11) Conditions or reasons for withdrawal from the study
12) Statements that the clinical research associates, responsible auditors, IRB, and regulatory authorities can access source documents; that in such a case, the subject's privacy will be protected; and that the subject is deemed to have consented to such access by writing his/her name and affixing his/her seal on or signing the consent form
13) A statement that the subject's privacy will be protected even if the results of the study are published
14) Details of expenses the subject needs to pay, if any
15) Details of payment to the subject, if any
16) Name, title, and contact information of the investigator or subinvestigator
17) Contact information of the study center in the event that the subject requires further information regarding the study or the rights of subjects, or in the event of study-related injury
18) Responsibilities of subjects
19) The type of IRB that evaluates and reviews the appropriateness of the study, items to be evaluated and reviewed by the IRB, and other matters regarding the IRB in relation to the study

15.4 Informed Consent for Pharmacogenomics/Biomarker Study

The investigator or subinvestigator will explain the details of the study listed below to subject candidates in a readily understandable way to confirm their willingness to provide consent to participate in the biomarker study by their free will, and obtain the result in writing. The informed consent forms for the core clinical study and the biomarker study will be prepared in a one-unit format. The investigator or subinvestigator will ensure that the subject's decision on the consent has been entered in the concerned section of the informed consent form.

1) Characteristics and properties of genetic information
2) Study objectives
3) Study methods
4) Foreseeable physical and mental benefits and risks associated with the study
5) Statements that participation in the pharmacogenomics study is based on the subject's own free will and that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she withdraws his/her consent; that participation in the core study will not be affected by

refusal to participate in the biomarker study.

6) Handling of specimens and data after withdrawal of consent
7) Matters on the method of handling, duration of storage, and disposal of specimens
8) Compensation and treatment that the subject can receive
9) Disclosure of study results and to whom the results belong
10) Details of expenses the subject needs to pay, if any
11) A statement that no payment is made for specimens provided by the subject
12) Protection of human rights, including the subject's privacy

15.5 Provision of New Information Affecting the Conduct of the Study

If any information that may affect the subject's willingness to participate in the study is obtained, the investigator or subinvestigator will promptly inform the subject and confirm the subject's willingness to continue participation in the study. The investigator or subinvestigator will also document the date of explanation, the person who has given the explanation, the details of the explanation, the subject's decision, and the date of confirming the subject's willingness in the medical record, etc. The investigator will promptly revise the consent form and subject information form, as necessary, and submit them to the sponsor. The investigator will also report the revised forms to the head of the study center and gain approval by the IRB. When any subjects are already participating in the study as of the time of approval by the IRB, the investigator or subinvestigator will obtain their consent to continue participation in the study again in the same manner as the above-mentioned procedure using the revised consent form and subject information form. A copy of the consent form and subject information form will be provided to the subjects. The original informed consent form will be retained at the study center. The investigator or subinvestigator will document (eg, in the original consent form or medical record) that a copy of the consent form and subject information form have been provided to the subject.

15.6 Planned Study Period

1 Jul 2016 to 31 Dec 2017

15.7 Protocol Amendment

If an amendment to the clinical study protocol is considered after the start of the study, the sponsor will examine the appropriateness of the amendment and potential influences on the study results through discussion with the medical expert, etc., if necessary, and

determine whether to make the amendment or not. The sponsor will clearly document and retain the content of the discussion, the presence or absence of the amendment, and the reason, etc.
The sponsor will promptly notify the investigator of the specific details of the amendment to the protocol. If the protocol is updated to a new version, the sponsor will newly obtain written agreement of the investigator and implement the procedures specified by the study center.

15.8 Permanent or Temporary Discontinuation of the Study

If any of the following occur and the sponsor judges that continuation of the study is difficult, the sponsor will temporarily discontinue the study. The sponsor will then determine whether to permanently discontinue the entire study, 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

If the sponsor decides to discontinue the study entirely after consultation with the medical expert etc., the sponsor will promptly notify the head of the study center in writing and the reason for the discontinuation. The head of the study center will promptly notify the investigator and the IRB in writing of the information obtained from the sponsor.
If the study is discontinued permanently or temporarily, 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.

15.9 Procedures for Preparing the Case Report Form and Remarks

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. The procedure for preparation of measurement reports by each measurement facility will be specified separately.

15.9.1 Style of the Case Report Form

In this study, an electronic CRF will be recorded using the electronic data capturing

(EDC) system ("Table 15.9-1 EDC System"), 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 15.9-1 EDC System

EDC system name	Medidata Rave®
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	Medidata Rave® 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

15.9.2 Completion of the Case Report Forms

The investigator will take an electronic signature training program prior to preparation of the CRF and the training record will supersede the list of signatures and printing of seals.

1) The CRF will be completed for subjects who provide informed consent.
2) The investigator or subinvestigator will complete the CRF in accordance with the "Guidance for Completing and Making Corrections to the Case Report Form" provided by the sponsor.
3) The study staff will follow the instructions of the investigator or subinvestigator when assisting with the completion of the CRF.
4) The investigator will submit the CRF to the sponsor and retain a copy of the CRF.
5) If there are any inconsistencies between the data in the CRF and the source documents, the investigator will separately prepare a record explaining the reason and submit it to the sponsor, and retain a copy of the record.

15.9.3 Signature or Seal with Printed Name Applied to the Case Report Form

The investigator will check all CRFs prepared at the study center, and affix his/her electronic signature to them.

15.9.4 Changes or Corrections to the Case Report Form

1) Any corrections to the CRF will be made by the investigator, subinvestigator, or

study staff in accordance with the "Guidance for Completing and Making Corrections to the Case Report Form" provided by the sponsor.

2) The investigator is responsible for the descriptions in the CRF, and will retain copies of all records, including changes or corrections.

15.10 Retention of Source Documents and Other Records

15.10.1 Definition of Source Documents

Source documents shall refer to original documents, data, and records set forth in ICH-GCP 1.52, or their certified copies, and include records (source data) necessary to reproduce and evaluate the factual progress of the clinical study. Source documents include hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, administration records, data recorded by automated measuring instruments, reproductions or transcripts verified as precise copies, microfiches, photographic negatives, microfilms or magnetic media, X-ray films, subject files, and records kept at either a pharmacy, laboratory, or medical technology department involved in the study.

15.10.2 Record Keeping

15.10.2.1 Institutional Review Board

The founder of the IRB will retain the standard operating procedures, member list, documents submitted, minutes and summaries of meetings, letters, etc., until the date specified in 1) or 2) below, whichever is later. However, if longer retention is requested by the sponsor, the duration and method of retention will be discussed with the sponsor.

1) Date of approval of quizartinib (or if clinical development is discontinued, 3 years after the date of notification of the discontinuation by the sponsor)
2) Three years after discontinuation or completion of the study

15.10.2.2 Study Center

The head of the study center or the person responsible for record keeping will retain the "documents or records related to the clinical study" to be retained by the study center until the date specified in 1) or 2) below, whichever is later. However, if longer retention is requested by the sponsor, the duration and method of retention will be discussed with the sponsor. A person responsible for record keeping will be designated for each set of records.

The head of the study center or the person responsible for record keeping will take

measures to prevent loss or disposal of these records during the relevant period and provide immediate access to them upon request.

1) Date of approval of quizartinib (or if clinical development is discontinued, 3 years after the date of notification of the discontinuation from the sponsor)
2) Three years after discontinuation or completion of the study

15.10.2.3 Sponsor

The sponsor will retain the "documents or records related to the clinical study" to be retained until the date specified in 1) or 2) below, whichever is later.

1) Five years after the date of approval of quizartinib (or if clinical development is discontinued, 3 years after the date of the decision on discontinuation) or the date of completion of the reexamination, whichever is later
2) Three years after discontinuation or completion of the study

15.11 Source Document Verification

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.

15.12 Organization

This study will be conducted under the organization described below. Each person with responsibilities defined below will perform his/her duties in accordance with the "Procedures for Task Assignment in the Study Organization" of Daiichi Sankyo Co., Ltd.

15.12.1 Sponsor

Daiichi Sankyo Co., Ltd.
3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan

PPD PPD

Clinical study director: PPD Director, Oncology Clinical Development

Department

Clinical Study Lead: PPD Oncology Clinical Development Department

Delivery Lead: PPD Oncology Clinical Development Department

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

PPD PPD

Person responsible for study drug management:

PPD CMC Planning Department

Person responsible for biostatistical analysis:

PPD Clinical Data & Biostatistics Department

Person responsible for pharmacokinetic analysis:

PPD Translational Medicine & Clinical Pharmacology Department

Person responsible for concentration measurement:

PPD Translational Medicine & Clinical Pharmacology Department

Person responsible for data management:

PPD Clinical Data & Biostatistics Department

Person responsible for quality management:

PPD Development Function

Person responsible for safety information:

PPD Pharmacovigilance Department

Person responsible for measures for handling of safety information:

PPD Pharmacovigilance Department

Person responsible for genome/gene analysis:

PPD Translational Medicine & Clinical Pharmacology Department

15.12.2 Medical Expert

PPD Oncology Clinical Development Department, Daiichi Sankyo Co., Ltd.

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

PPD PPD

Duties: The medical expert will give advice on medical issues during planning and conduct of the study, and preparation of the clinical study report. The medical expert will affix his/her signature to the clinical study report if he/she is assessed

to be appropriate as an authorizer of the report.

15.12.3 EDC System Development

Medidata Solutions, Inc.
Person responsible: PPD Chairman & Chief Executive Officer
350 Hudson Street, 9th Floor, New York, New York 10014, USA
PPD PPD
Duties: The company will perform operation, management, and maintenance of the EDC system according to the consignment contract.

15.12.4 EDC System Support

Fujitsu Systems East Limited
Person responsible: PPD
Shinagawa Season Terrace, 1-2-70 Konan, Minato-ku, Tokyo 108-0075, Japan
PPD PPD
Duties: The company will perform EDC system support activities according to the consignment contract.

15.12.5 Contract Research Organization

Mediscience Planning Inc.
Person responsible: PPD Director, Ninth Department of Clinical Development
1-11-44 Akasaka, Minato-ku, Tokyo 107-0052, Japan
PPD PPD

15.12.6 Study Center and Investigator

Refer to Attachment 2.
Duties: To agree on the protocol, the investigator will prepare and revise the informed consent form, select subjects and obtain their consent, instruct and supervise the subinvestigators and study staff, provide materials and information, cooperate with monitoring and auditing, report deviations of or changes from the protocol and AEs, complete the CRFs, and retain the “documents or records related to the clinical study” in consultation with the sponsor.

15.12.7 Central Laboratory

15.12.7.1 Measurement of Drug Concentrations

BASi corporate

Person responsible: PPD

2701 Kent Avenue, West Lafayette, IN 47906, USA

PPD PPD

Duties: The company will measure and store the specimens sent from each study center according to the consignment contract.

15.12.7.2 Measurement of Pharmacodynamic Endpoints

1) Analysis of FLT3-ITD status and c-KIT mutations

SRL, Inc.

Person responsible: PPD

2-1-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 163-0409, Japan

PPD PPD

Duties: The company will perform analyses of FLT3-ITD status and c-KIT mutations.

2) Measurement of phosphorylated FLT3, STAT5, and c-KIT protein levels in blood

Shin Nippon Biomedical Laboratories, Ltd.

Person responsible: PPD

2438 Miyanoura-cho, Kagoshima-shi, Kagoshima 891-1394, Japan

PPD PPD

Duties: The company will measure phosphorylated FLT3, STAT5, and c-KIT protein levels in the blood according to the contract with the sponsor.

3) Measurement of inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein

Shin Nippon Biomedical Laboratories, Ltd.

Person responsible: PPD

2438 Miyanoura-cho, Kagoshima-shi, Kagoshima 891-1394, Japan

PPD PPD

Duties: The company will measure the inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein according to the contract with the sponsor.

4) Confirmation of 12-lead ECG measurement results, etc.

eResearchTechnology, Inc.
Person responsible: PPD
1818 Market Street, Suite 1000, Philadelphia, PA 19103, United States
PPD PPD
Duties: The company will confirm the ECG measurement results submitted by each study center, etc. according to the contract with the sponsor.

15.12.7.3 Agency to Collect Specimens for Measurement of Drug Concentrations and Pharmacodynamic Endpoints, etc.

1) LSI Medience Corporation
Person responsible: PPD
3-30-1 Shimura, Itabashi-ku, Tokyo 174-8555, Japan
PPD PPD
Duties: Concerning specimens for drug concentration measurement and the biomarker study (phosphorylated FLT3, STAT5, and c-KIT protein levels in blood, and the inhibitory activity of plasma quizartinib on phosphorylated FLT3 protein), the company will collect the specimens from the study center, store and anonymize the specimens, and send them to each laboratory according to the contract with the sponsor.

2) SRL Medisearch Inc.
Person responsible: PPD
6-5-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 163-1310, Japan
PPD PPD
Duties: Concerning specimens for the biomarker study (FLT3-ITD status and c-KIT mutations), the company will collect the specimens from the study center, store and anonymize the specimens, and send them to each laboratory according to the contract with the sponsor.

15.12.8 Department Responsible for Audit

Person responsible: PPD R&D & PV Quality Assurance Department, Quality & Safety Management Division, Daiichi Sankyo Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
PPD PPD
Duties: The department will perform GCP auditing.

15.13 Emergency Contact Information

1) Night hours (18:00 to 9:00) and Saturdays, Sundays, and holidays (all day):

PPD Oncology Clinical Development Department, Daiichi Sankyo Co., Ltd.
PPD

2) Daytime (9:00 to 18:00) from Monday through Friday (except holidays):

PPD Oncology Clinical Development Department, Daiichi Sankyo Co., Ltd.
PPD PPD

16. REFERENCES

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17) Revision of the Guidelines for the Clinical Evaluation of Anticancer Drugs. PFSB/ELD Notification No. 1101001 (1 Nov 2005).

18) Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; Ministry of Economy, Trade and Industry. Ethical Guidelines for Human Genome/Gene Analysis Research. (established on 29 Mar 2001, fully rev. on 28 Dec 2004, partially rev. on 29 Jun 2005, partially rev. on 1 Dec 2008, fully rev. on 8 Feb 2013).

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17. APPENDICES

Appendix 1 ECOG Performance Status (PS)

Appendix 2 New York Heart Association (NYHA) Functional Classification

Appendix 3 SAVER FORM

Appendix 4 Exposure in Utero Reporting Form

Attachments

Attachment 1	Subject Registration Form
Attachment 2	List of Study Centers and Investigators
Attachment 3	Cylocide® Injection 20 mg / 40 mg / 60 mg / 100 mg / 200 mg [package insert]. Nippon Shinyaku Co., Ltd.; Dec 2014.
Attachment 4	Cylocide®N Injection 400 mg / 1 g [package insert]. Nippon Shinyaku Co., Ltd.; Dec 2014.
Attachment 5	Daunomycin® for Injection 20 mg [package insert]. Meiji Seika Pharma Co., Ltd.; Apr 2011.
Attachment 6	Idamycin® for Intravenous Use 5 mg [package insert]. Pfizer Japan Inc.; Jun 2009.

[Appendix 1]

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 2]

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 3] SAVER FORM

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

When completed, send to Daiichi-Sankyo.

Supplemental pages used *(Mark all that apply)*: ☐ SAE ☐ Lab Results ☐ Concomitant Medications

Report Type: ☐ Initial ☐ Follow-up #

1. Source

Investigator Name: _____ **Country:** _____

Address: _____

Phone #: _____ **Fax #:** _____

2. Subject and Study Information

Screening #/Subject #: _____ **Randomization #:** _____ **Subject Initials:** _____

Birth Date: *(dd Mmm yyyy)* _____ **Gender:** ☐ Male ☐ Female

Weight: ☐ kg ☐ lb _____ **Height:** ☐ cm ☐ in _____

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Race: ☐ Asian ☐ Black ☐ Caucasian ☐ American Indian/Alaskan Native
☐ Native Hawaiian/Pacific Islander ☐ Other _____

Phase of Study at time of SAE: ☐ Screening ☐ Washout ☐ Placebo/Run-in
☐ Randomized ☐ Post Study ☐ Open-label

Date of Informed Consent: *(dd Mmm yyyy)* _____

3. Primary Serious Adverse Event

(Use appropriate medical terminology, symptoms should be grouped together as syndromes and diagnosis.)

If additional events are reported, use supplemental page. If supplemental SAE pages were used, mark here: ☐

SAE (Event/Diagnosis): _____

Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	NCI CTCAE Severity Grading	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ 1=Mild ☐ 2=Moderate ☐ 3=Severe ☐ 4=Life-threatening or disabling ☐ 5=Death	☐ Recovered/Resolved ☐ Recovering/Resolving ☐ Not Recovered/Not Resolved ☐ Recovered/Resolved with sequelae /residual effect(s) present ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐
	☐	☐

4. In Case of Death

Date: *(dd Mmm yyyy)* _____ **Autopsy:** ☐ Yes ☐ No

Certificate: ☐ Yes ☐ No **Cause:** _____

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

5. Study Drug Dosing

*Record only dose given to subject **at time of SAE.** Complete all previous dosing regimes including placebo run-in Section 6.*

Study Drug Dosing						Study Drug Action Taken				
Study Drug	**Unit Dose**	**Frequency**	**Route**	**Start Date** *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*	**None**	**Discontinued**	**Reduced**	**Interrupted**	**Increased**
						☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐

Was the subject withdrawn due to SAE? ☐ Yes ☐ No

Was Study Drug Code broken due to SAE? ☐ Yes ☐ No If Yes, Date: *(dd Mmm yyyy)* _____

Who: _____ Drug: _____ Dosing: _____

6. Previous Study Drug Dosing Regimens per Protocol, including placebo run-in.

Study drug dosing at the time of SAEs is captured in Section 5. ***Do NOT complete with "See Attached".***

If not applicable mark here: ☐

Drug Name	Unit Dose	Frequency	Route	Start Date *(dd Mmm yyyy)*	Stop Date *(dd Mmm yyyy)*

7. Relevant Concomitant Medications

(Include those taken before the onset of the event, not taken as a treatment for the event.) ***Do NOT complete with "See Attached".*** If Supplemental Concomitant Medication page is used, mark here: ☐

Generic/Brand Name	Dose	Frequency	Route	Start Date *(dd Mmm yyyy)*	Stop Date *(dd Mmm yyyy)*	Indication	Continuing?
							☐
							☐
							☐
							☐
							☐
							☐

8. Relevant Lab Results

Do NOT complete with "See Attached." If supplemental Lab Results pages were used, mark here: ☐

Lab Test	Date *(dd Mmm yyyy)*	Results	Reference Normal Range (Units)

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

9. Relevant Medical History Including Allergies

Do NOT complete with "See Attached."

Date of Onset *(dd Mmm yyyy)*	Current *(Mark one only)*	Past *(Mark one only)*	Description
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

10. Narrative

Record a detailed description of the event including the course of the event, evaluation, assessment and treatment.

11. Person Completing This Form

Name _____ **Signature** _____ **Date** _____

Title _____ **Phone Number** _____

Investigator Name _____ **Signature** _____ **Date** _____

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES (Supplemental SAE)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

SAE (Event/Diagnosis) #: 2 _____
Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	NCI CTCAE Severity Grading	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ 1=Mild ☐ 2=Moderate ☐ 3=Severe ☐ 4=Life-threatening or disabling ☐ 5=Death	☐ Recovered/Resolved ☐ Recovering/Resolving ☐ Not Recovered/Not Resolved ☐ Recovered/Resolved with sequelae /residual effect(s) present ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐

SAE (Event/Diagnosis) #: 3 _____
Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	NCI CTCAE Severity Grading	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ 1=Mild ☐ 2=Moderate ☐ 3=Severe ☐ 4=Life-threatening or disabling ☐ 5=Death	☐ Recovered/Resolved ☐ Recovering/Resolving ☐ Not Recovered/Not Resolved ☐ Recovered/Resolved with sequelae /residual effect(s) present ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐

SAE (Event/Diagnosis) #: 4 _____
Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	NCI CTCAE Severity Grading	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ 1=Mild ☐ 2=Moderate ☐ 3=Severe ☐ 4=Life-threatening or disabling ☐ 5=Death	☐ Recovered/Resolved ☐ Recovering/Resolving ☐ Not Recovered/Not Resolved ☐ Recovered/Resolved with sequelae /residual effect(s) present ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES
(Supplemental Concomitant Medications)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

7. Relevant Concomitant Medications (Continued)
(Include those taken before the onset of the event, not taken as a treatment for the event.) ***Do NOT complete with "See Attached".***

Generic/Brand Name	Dose	Frequency	Route	Start Date *(dd Mmm yyyy)*	Stop Date *(dd Mmm yyyy)*	Indication	Continuing?
							☐
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SERIOUS ADVERSE EVENT REPORT (SAVER) FORM-ONCOLOGY STUDIES
(Supplemental Lab Results)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

8. Relevant Lab Results (Continued)
Do NOT complete with "See Attached."

Lab Test	Date *(dd Mmm yyyy)*	Results	Reference Normal Range (Units)

[Appendix 4] Exposure in Utero Reporting Form

EXPOSURE IN UTERO REPORTING FORM

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

When completed, send to Daiichi-Sankyo.
Supplemental pages used *(Mark all that apply)*: ☐ Lab Results ☐ Concomitant Medications

1. Source

Contact Information: ☐ Initial ☐ Follow-up # _____ Was a SAVER form also completed? ☐ Yes ☐ No

Investigator Name: _____ **Country:** _____

Address: _____

Phone #: _____ **Fax #:** _____

2. Subject and Study Information

Screening #/Subject #: _____ **Randomization #:** _____ **Subject Initials:** _____

Birth Date: *(dd Mmm yyyy)* _____ **Gender:** ☐ Male ☐ Female

Weight: ☐ kg ☐ lb _____ **Height:** ☐ cm ☐ in _____

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Race: ☐ Asian ☐ Black ☐ Caucasian ☐ American Indian/Alaskan Native
☐ Native Hawaiian/Pacific Islander ☐ Other

Phase of Study at time of SAE: ☐ Screening ☐ Washout ☐ Placebo/Run-in
☐ Randomized ☐ Post Study ☐ Open-label

Date of Informed Consent: *(dd Mmm yyyy)* _____

3. Male Subject's Partner's Information

If the subject is male, complete the column below regarding the subject's partner's information.

Birth Date: *(dd Mmm yyyy)* _____

Weight: ☐ kg ☐ lb _____ **Height:** ☐ cm ☐ in _____

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Race: ☐ Asian ☐ Black ☐ Caucasian ☐ American Indian/Alaskan Native
☐ Native Hawaiian/Pacific Islander ☐ Other

4. Method(s) of Contraception During Study Participation

Methods and dates should be obtained from the study subject when the pregnancy of female subject or male subject's partner is identified and not taken only from the case report form. Include all methods used prior to and during study participation.

		Start Date *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*
☐ Abstinence			
☐ Oral Contraceptive, specify drug	_____	_____	_____
☐ Other, specify method	_____	_____	_____

Was subject taking study drug at the time of conception? *(Mark one)* ☐ Yes ☐ No

EXPOSURE IN UTERO REPORTING FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

5. Pregnancy Status

If the subject is male, complete the column below regarding the subject's partner's pregnancy status.

Onset Date of Last Menstrual Period: *(dd Mmm yyyy)* _____

Expected Date of Delivery: *(dd Mmm yyyy)* _____

Estimated Gestational Age When Pregnancy Diagnosed: _____ Weeks

Method of Diagnosis: _____

Prenatal testing performed: *(Mark one)* ☐ Yes ☐ No

If yes, specify:	**Findings**	**Date** *(dd Mmm yyyy)*
☐ Ultrasound		
☐ Amniocentesis		
☐ Other (specify) _____		

Number of: **Previous Pregnancies** _____ **Congenital Anomalies** _____

Normal Births _____ **Abortions or Miscarriages** _____

6. Study Drug Dosing

Study Drug Dosing						**Study Drug Action Taken**				
Study Drug	**Unit Dose**	**Frequency**	**Route**	**Start Date** *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*	**None**	**Discontinued**	**Reduced**	**Interrupted**	**Increased**
						☐	☐	☐		☐
						☐	☐	☐		☐
						☐	☐	☐		☐

Was Study Drug Code broken? ☐ Yes ☐ No If Yes, Date: *(dd Mmm yyyy)* _____

Who: _____ Drug: _____ Dosing: _____

7. Relevant Concomitant Medications

If the subject is male, complete the column below regarding the subject's partner's relevant concomitant medications.

Generic/Brand Name	**Dose**	**Frequency**	**Route**	**Start Date** *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*	**Indication**	**Continuing?**
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐

EXPOSURE IN UTERO REPORTING FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

8. Relevant Lab Results

Do NOT complete with "See Attached."

If the subject is male, complete the column below regarding the subject's partner's relevant lab results.

If supplemental Lab Results pages were used, mark here: ☐

Lab Test	Date *(dd Mmm yyyy)*	Results	Reference Normal Range (Units)

9. Relevant Maternal Medical History

If the subject is male, complete the column below regarding the subject's partner's relevant maternal medical history.

Tobacco Use: ☐ Non-Smoker ☐ Current Smoker: number of cigarettes/day _____

Alcohol Use: _____

History of elicit drug use: _____

History of sexually transmitted disease: _____

Other relevant medical history: _____

10. Pregnancy Outcome

If the subject is male, complete the column below regarding the subject's partner's pregnancy outcome.

Fetal Outcome:
(Mark only ONE outcome)

Birth: ☐ Live ☐ Still

Actual date of delivery: *(dd Mmm yyyy)* _____

Abortion: ☐ Spontaneous ☐ Induced

Date of abortion: *(dd Mmm yyyy)* _____

Type of Delivery: ☐ Vaginal ☐ Cesarean

Gender: ☐ Male ☐ Female

Infant weight (lbs.): _____

Infant length (inches): _____

Apgar Score: _____

Head Circumference (inches): _____

Any physical abnormalities noted: _____

EXPOSURE IN UTERO REPORTING FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

11. Exposure in Utero Supplemental Information

Record any additional information in the space below. If the subject is male, include any additional information on the subject's partner (and also the partner himself if necessary).

12. Investigator Signature

Investigator Name	**Signature**	**Date**