CLINICAL STUDY PROTOCOL

A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF QUIZARTINIB ADMINISTERED IN COMBINATION WITH INDUCTION AND CONSOLIDATION CHEMOTHERAPY, AND ADMINISTERED AS CONTINUATION THERAPY IN SUBJECTS 18 TO 75 YEARS OLD WITH NEWLY DIAGNOSED FLT3-ITD (+) ACUTE MYELOID LEUKEMIA

AC220-A-U302

QUIZARTINIB ADVANCEMENT INTO THE NEXT GENERATION OF TRIALS FOR UNMET NEEDS IN AML – First-LINE (QuANTUM-First)

IND/EudraCT NUMBER 74,552/2015-004856-24

VERSION 7.0, 26 May 2021

DAIICHI SANKYO INC
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United States

INVESTIGATOR AGREEMENT

A Phase 3, Double-Blind, Placebo-Controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First)

Sponsor Approval:

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

PPD	PPD
Print Name	**Sig**
Senior Director, Clinical Development Oncology	26 MAY 2021
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

DOCUMENT HISTORY

Version Number	Version Date
7.0	26 May 2021
6.0	28 Oct 2020
5.0	07 Apr 2020
4.0	26 Jun 2019
3.0	20 Nov 2018
2.0	06 Apr 2017
1.0	17 Dec 2015

SUMMARY OF CHANGES

Amendment Rationale:

The main purpose of this amendment is to update the hierarchical order for statistical testing of the secondary endpoints based on recent feedback from the United States Food and Drug Administration (FDA).

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of subjects nor the scientific value of the study.

Changes to the Protocol:

Please refer to the comparison document for protocol Version 7.0 (dated 26 May 2021) versus Version 6.0 (dated 28 Oct 2020) for actual changes in-text. The Summary of Changes below is a top-line summary of major changes in the current AC220-A-U302 clinical study protocol (Version 7.0) by section.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes.
Minor edits, such as updates to language that do not alter original meaning, update to version numbering, formatting, change in font color, deletions of unused references, additions of new references, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or changes in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Synopsis, Statistical Analyses 11.4.1.2 Secondary Efficacy Analyses	Changed the statistical testing order of the secondary endpoints and clarified that the EFS analysis which uses the IRC assessment will be based on the EFS definition in new health authority Guidances.[63,72]	Updated based on recent FDA recommendation.
3.1. Overall Design	Figure 3.2, days of cytarabine dosing corrected	Correction
17.1.1. Schedule of Events – Induction Phase	Table 17.3: Schedule of Assessment - Induction Phase (Cycle 2 with "5+2" regimen) - added footnote for EORTC QLQ-C30 and EQ-5D-5L only to be done if it is the last day of the Induction Phase for Cycle 2, Day 28, to match Section 6.2.1.2.2.11.	Correction

EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = health-related quality of life questionnaire; IRC = Independent Review Committee; QLQ-C30 = core quality of life questionnaire

PROTOCOL SYNOPSIS

EudraCT:	2015-004856-24
IND Number:	74,552
Protocol Number:	AC220-A-U302
Investigational Product:	Quizartinib
Active Ingredient(s) / INN:	Quizartinib dihydrochloride / Quizartinib
Study Title:	A Phase 3, Double-Blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First)
Study Phase:	Phase 3
Indication Under Investigation:	Newly diagnosed FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) (+) acute myeloid leukemia (AML)
Study Objectives:	**Primary Objective:** The primary objective is to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of overall survival (OS) in subjects with newly diagnosed AML with FLT3-ITD mutations. **Secondary Objectives:** The secondary objectives are to: • Compare the following in subjects treated with quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles): – Event-free survival (EFS) – Composite complete remission rate (CRc = complete remission (CR) + CR with incomplete neutrophil or platelet recovery [CRi]) after Induction; – Percentage of subjects achieving CRc with FLT3-ITD minimal or measurable residual disease (MRD) negativity after Induction;

  - Complete remission (CR) rate after Induction;
  - Percentage of subjects achieving CR with FLT3-ITD MRD negativity after Induction.
- Further characterize the safety profile of quizartinib administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles.
- Assess the pharmacokinetics (PK) of quizartinib and its metabolite (AC886).

Exploratory Objectives:

The exploratory objectives are to:

- Evaluate the following in subjects treated with quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles):
  - Relapse-free survival (RFS);
  - Duration of complete remission (CR);
  - CR rate at end of first Induction Cycle;
  - CRc rate at the end of first Induction Cycle;
  - Rate of CR with partial hematologic recovery (CRh) after Induction (only for Independent Review Committee [IRC] assessment of response);
  - Rate of morphologic leukemia-free state (MLFS) after Induction (only for IRC assessment of response);
  - RFS in subjects who enter the Continuation Phase, after achieving CRc in Induction;
  - Transplantation rate;
  - Heath care resource utilization;
  - Impact on subject reported quality of life (QoL) and symptoms, as assessed by European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30);
  - Change in general health status measured by EQ-5D-5L.
- Assess the population PK (PopPK) of quizartinib and exposure-response relationship for QT interval corrected with Fridericia's formula (QTcF) including assessment

	post-anthracycline administration, and clinical response measures. • Assess the pharmacodynamics and biomarkers of quizartinib.
Study Design:	This is a Phase 3, randomized, double-blind, placebo-controlled, global study to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of OS in subjects with newly diagnosed AML with FLT3-ITD mutations. Randomization will be stratified based on: • Region (North America, Europe, and Asia/Other Regions) • Age (<60 years old, ≥60 years old) • White blood cell (WBC) count at the time of diagnosis of AML (<40×10^9/L, ≥40×10^9/L) **Study Phases:** **<u>Induction Phase (up to 2 cycles)</u>** <u>Cycle 1</u> Cycle 1, Day 1 is defined as the start date of the chemotherapy infusions. Cytarabine (cytosine arabinoside) 100 mg/m^2/day (200 mg/m^2/day allowed if institutional or local standard) will be administered by continuous intravenous (IV) infusion for a total of 7 days, starting on Day 1 and ending on Day 8. One of the following anthracycline regimens (investigator's choice) will be administered: Daunorubicin 60 mg/m^2/day IV infusion on Days 1, 2, and 3; or Idarubicin 12 mg/m^2/day IV infusion on Days 1, 2, and 3. Subjects will be randomized on Day 7. If necessary, Randomization may be performed later (eg, Days 8 to 10) to allow time for addressing electrolyte abnormalities, QTcF prolongation, etc. Quizartinib/placebo will be administered orally once daily for 14 days. Dosing should start after the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to start within 3 days of Randomization if possible. If quizartinib/placebo cannot

be started within 3 days of Randomization, please contact the Medical Monitor. The dose will be 40 mg/day. For subjects concomitantly receiving a strong cytochrome P450 (CYP) 3A4 inhibitor, the dose will be reduced from 40 mg/day to 20 mg/day. If quizartinib/placebo is interrupted, missed doses will not be made up.

On Day 21 (window Day 21 to Day 28), a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected for local and central pathology. If this bone marrow does not provide an accurate assessment of response, the bone marrow aspiration will be repeated upon count recovery or Day 56 (± 3 days), whichever occurs first. Subjects with ≥ 5% blasts after Cycle 1 may receive a second cycle of Induction, if appropriate.

Cycle 2

For Cycle 2 of Induction, investigators may choose to administer 1 of the following:

"7+3" chemotherapy regimen, defined as 7 days of continuous IV infusion of cytarabine 100 mg/m^2/day (200 mg/m^2/day allowed if institutional or local standard) plus 3 days of anthracycline (the same anthracycline must be used throughout the Induction phase); OR

"5+2" chemotherapy regimen, defined as 5 days of continuous IV infusion of cytarabine 100 mg/m^2/day (200 mg/m^2/day allowed if institutional or local standard) plus 2 days of anthracycline (the same anthracycline must be used throughout the Induction phase).

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will start following the end of the cytarabine infusion, normally on Cycle 2, Day 8 or Cycle 2, Day 6, depending on the chemotherapy regimen selected by the investigator (ie, "7+3" or "5+2", respectively). If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

Collection of a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) and assessment of response will be done according to the same schedule as in Cycle 1.

Consolidation Phase

Subjects who achieve a CR or CRi at the end of the Induction Phase will enter the Consolidation Phase. The following are the options for consolidation therapy:

- treatment with quizartinib/placebo plus cytarabine (4 cycles, if tolerated); or
- allogeneic hematopoietic stem cell transplantation (HSCT); or
- treatment with quizartinib/placebo plus cytarabine, followed by allogeneic HSCT.

Cytarabine will be given on Days 1, 3, and 5 for a total of 6 doses. The cytarabine regimen will be:

- for subjects <60 years old: cytarabine 3.0 g/m^2 IV infusion, every 12 hours; or
- for subjects ≥60 years old: cytarabine 1.5 g/m^2 IV infusion, every 12 hours.

Quizartinib/placebo will be administered orally once daily for 14 days, starting on Day 6. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. The dose will be 40 mg/day. For subjects concomitantly receiving a strong cytochrome CYP3A4 inhibitor, the dose will be reduced from 40 mg/day to 20 mg/day. If quizartinib/placebo is interrupted, missed doses will not be made up.

A bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected for local and central pathology in the first and last cycles of Consolidation, upon count recovery from Day 21 to Day 56.

Allogeneic Hematopoietic Stem Cell Transplantation

Subjects are permitted to undergo allogeneic HSCT between the end of the Induction Phase and the start of the Continuation Phase. Under certain circumstances, subjects meeting necessary criteria may undergo allogeneic HSCT for consolidation within the first 3 months of the Continuation Phase (see Section 6.2.2.2).

For subjects who undergo allogeneic HSCT, treatment with quizartinib/placebo should be discontinued 7 days before the start of a conditioning regimen. Subjects may begin continuation therapy 30 to 180 days after the allogeneic HSCT.

Sites should follow their local procedures for allogeneic HSCT conditioning and recovery.

From the time of allogeneic HSCT up through the end of the allogeneic HSCT period, the investigator will contact the transplant unit every 4 weeks for follow-up information. Once the subject is able, the subject will return to the clinic for site visits every 4 weeks.

Continuation Phase (up to 36 cycles):

Following consolidation therapy, subjects will enter the Continuation Phase if they meet the inclusion criteria. In addition, per investigator discretion, subjects who have achieved CR or CRi following Induction but are unable to receive consolidation therapy will be permitted to enter the Continuation Phase if they meet the inclusion criteria.

During the Continuation Phase subjects will be treated with quizartinib/placebo once daily for up to 36 cycles. Continuation therapy will begin after induction or consolidation therapy, including allogeneic HSCT, and will continue until relapse, start of nonprotocol specified AML treatment, death, unacceptable toxicity, study close, or completion of 36 cycles, whichever occurs first.

Quizartinib/placebo will be administered orally once daily starting on Day 1, with no breaks in dosing between cycles. If quizartinib/placebo is interrupted, missed doses will not be made up.

The starting dose will be 30 mg. For subjects receiving a strong CYP3A4 inhibitor concomitantly, the starting dose will be 20 mg/day.

On Cycle 1, Day 16, the dose will be increased from 30 mg/day to 60 mg/day (from 20 mg/day to 30 mg/day for subjects receiving a strong CYP3A4 inhibitor) if the average QTcF of the triplicate electrocardiograms (ECGs) is ≤450 ms on Cycle 1, Day 15. If the dose of quizartinib/placebo is not able to be increased on Cycle 1, Day 16, the dose may be increased on Cycle 2, Day 2 if the average QTcF of the triplicate ECGs is ≤450 ms on Cycle 2, Day 1. Once the dose is increased to 60 mg/day, the subject may continue on this dose as long as dose reduction is not needed.

Subjects will have their blood counts monitored every 4 weeks and will have a bone marrow exam every 12 weeks for 48 weeks and then every 24 weeks until week 96.

	Long-Term Follow-up Phase The Long-Term Follow-up Phase begins upon completion of 36 cycles of quizartinib/placebo in the Continuation Phase or permanent discontinuation of quizartinib/placebo in any phase. After completion of the 30 day safety visit, long-term follow-up visits will be performed as follows: • Every 4 weeks for subjects who have not had an EFS event; • Every 12 weeks for subjects who have had an EFS event.
Study Duration:	The total duration of subject participation will be until death, withdrawal of consent, the subject becomes lost to follow-up, or study closure, whichever occurs first. Subjects will be followed for EFS and OS events after completion of induction and consolidation therapy whether or not the subject receives continuation therapy. The total duration of treatment with quizartinib/placebo will be up to 42 cycles (inclusive of Induction, Consolidation, and Continuation Phases). The OS analysis will be performed: • When the target 287 OS events are observed and a minimum of 24 months has elapsed since the last subject was randomized. • If the target 287 OS events are not achieved by 24 months since the last subject was randomized, then the analysis will be performed at a maximum of 30 months after the last subject is randomized. All other efficacy analyses will be performed at the same time as the OS analysis. The primary completion date is the date when the final OS analysis (up to a maximum of 30 months after the last subject is randomized) has been completed. All subjects still on treatment and continuing to derive benefit from study drug at the primary completion date will continue to follow the study schedule of assessments until the overall End of Study is reached. Overall End of Study will occur when: • all subjects have discontinued treatment and discontinued long-term survival follow-up or have died • an alternative study becomes available, for subjects continuing to derive benefit from treatment with quizartinib, where the study drug is offered to these subjects

	• the study is discontinued by the Sponsor for other reasons (eg, administrative, program-level or class-related) The subject's EOS is the date of their last study visit/contact.
Study Centers and Location:	This study will be conducted in approximately 250 study sites worldwide.
Subject Eligibility Criteria:	**Inclusion Criteria:** Subjects must satisfy all of the following criteria to be randomized: 1. Must be competent and able to comprehend, sign, and date an Ethics Committee or Institutional Review Board approved Informed Consent Form (ICF) before performance of any study-specific procedures or tests; 2. ≥18 years or the minimum legal adult age (whichever is greater) and ≤75 years (at Screening); 3. Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm based on the World Health Organization (WHO) 2008 classification (at Screening); 4. Eastern Cooperative Oncology Group performance status 0-2 (at Screening); 5. Presence of FLT3-ITD activating mutation in bone marrow (allelic ratio of ≥3% FLT3-ITD/total FLT3); 6. Subject is receiving standard "7+3" induction chemotherapy regimen as specified in the protocol; 7. Adequate renal function defined as: a. Creatinine clearance rate >50 mL/min, as calculated with the modified Cockcroft Gault equation; 8. Adequate hepatic function defined as: a. Total serum bilirubin ≤1.5 × ULN unless the subject has documented Gilbert's syndrome or the increase is related to increased unconjugated (indirect) bilirubin due to hemolysis; b. Serum alkaline phosphatase, aspartate transaminase and alanine transaminase ≤2.5 × ULN; 9. Serum electrolytes within the institution's normal limits: potassium, calcium (total calcium, calcium corrected for serum albumin in case of hypoalbuminemia, or ionized calcium) and magnesium. If outside of the institution's

normal range, subject will be eligible when electrolytes are corrected;

10. If a woman of childbearing potential, must have a negative serum pregnancy test upon entry into this study and must be willing to use highly effective birth control upon enrollment, during the treatment period and for 6 months following the last dose of investigational drug or cytarabine, whichever is later. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy);
11. If male, must be surgically sterile or willing to use highly effective birth control upon enrollment, during the treatment period, and for 6 months following the last dose of investigational drug or cytarabine, whichever is later.

Exclusion Criteria:

Subjects who meet any of the following criteria are not eligible to be randomized:

1. Diagnosis of acute promyelocytic leukemia (APL), French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or BCR-ABL positive leukemia (ie, chronic myelogenous leukemia in blast crisis); subjects who undergo diagnostic workup for APL and treatment with all-trans retinoic acid (ATRA), but who are found not to have APL, are eligible (treatment with ATRA must be discontinued before starting induction chemotherapy).
2. Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms;
3. Prior treatment for AML, except for the following allowances:
    a. Leukapheresis;
    b. Treatment for hyperleukocytosis with hydroxyurea;
    c. Cranial radiotherapy for central nervous system (CNS) leukostasis;
    d. Prophylactic intrathecal chemotherapy;
    e. Growth factor/cytokine support;
4. Prior treatment with quizartinib or other FLT3-ITD inhibitors;

5. Prior treatment with any investigational drug or device within 30 days prior to Randomization (within 2 weeks for investigational or approved immunotherapy) or currently participating in other investigational procedures;
6. History of known CNS leukemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture is recommended for subjects with symptoms of CNS leukemia to rule out extramedullary CNS involvement;
7. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated with no evidence of disease for at least 2 years;
8. Uncontrolled or significant cardiovascular disease, including any of the following:
    a. Bradycardia of less than 50 beats per minute, unless the subject has a pacemaker;
    b. QTcF interval >450 ms;
    c. Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome);
    d. Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;
    e. History of clinically relevant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes);
    f. History of second (Mobitz II) or third degree heart block (subjects with pacemakers are eligible if they have no history of fainting or clinically relevant arrhythmias while using the pacemaker);
    g. History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to Screening;
    h. History of New York Heart Association Class 3 or 4 heart failure;
    i. Left ventricular ejection fraction (LVEF) ≤45% or less than the institutional lower limit of normal per multi-gated acquisition scan (MUGA) or echocardiogram done within 30 days prior to randomization;
    j. Complete left bundle branch block;
9. Active acute or chronic systemic fungal, bacterial, or viral infection not well controlled by antifungal, antibacterial or antiviral therapy;
10. Known active clinically relevant liver disease (eg, active hepatitis B, or active hepatitis C)

	11. Known history of human immunodeficiency virus (HIV). Subjects should be tested for HIV prior to Randomization if required by local regulations or EC; 12. History of hypersensitivity to any excipients in the quizartinib/placebo tablets; 13. Females who are pregnant or breastfeeding; 14. Otherwise considered inappropriate for the study by the investigator.
Dosage Form, Dose and Route of Administration:	Quizartinib is supplied to the Study Center as 20 mg and 30 mg tablets. Each 20 mg tablet contains 20 mg quizartinib dihydrochloride (17.7 mg free base), and each 30 mg tablet contains 30 mg quizartinib dihydrochloride (26.5 mg free base). Placebo tablets will match the appearance of quizartinib 20 mg and 30 mg tablets. The quizartinib 20 mg and matching placebo are white, film-coated, round tablets. The quizartinib 30 mg and matching placebo are yellow, film-coated, round tablets. Quizartinib/placebo is packaged in high density polyethylene bottles, containing 30 tablets each, with child-resistant caps.
Study Endpoints:	**Efficacy** The primary efficacy endpoint is OS. Overall survival is defined as the time from randomization until death from any cause. Secondary efficacy endpoints (ie, secondary outcome measures) are: • Event-free survival is defined as the time from Randomization until the date of the earliest of any of the following: – Refractory disease (or treatment failure) which is determined at the end of the Induction Phase; – Relapse after CR or CRi; – Death from any cause at any time during the study. • Composite complete remission rate which is the percentage of subjects achieving CR or CRi after Induction; • Percentage of subjects achieving CRc with FLT3-ITD MRD negativity below a certain cutoff after Induction. Minimal or measurable residual disease is the presence of a small

number of leukemic cells in the bone marrow of patients with AML below the level of detection using conventional morphologic assessment. The FLT3-ITD MRD assay by Next Generation Sequencing will be used to detect and quantify residual FLT3-ITD mutations.

- Complete remission rate, which is the percentage of subjects achieving CR after Induction;
- Percentage of subjects achieving CR with FLT3-ITD MRD negativity following induction therapy.

Exploratory efficacy endpoints are:

- RFS is the time from randomization, for subjects who achieve CR or CRi in the Induction Phase, until documented relapse or death from any cause, whichever comes first;
- Duration of CR is the time from the first documented CR until documented relapse or death from any cause, whichever comes first;
- CR rate at the end of the first Induction cycle is the percentage of subjects who achieved CR after 1 Cycle of Induction;
- CRc rate at the end of the first Induction cycle is the percentage of subjects whose best response is CR or CRi at the end of first Induction cycle;
- CRh rate is the percentage of subjects achieving CRh after Induction (only for IRC assessment of response);
- MLFS rate is the percentage of subjects achieving MLFS after Induction (only for IRC assessment of response);
- RFS in subjects who enter the Continuation Phase is the time from randomization, for subjects who achieve CR or CRi in the Induction Phase, until relapse or death from any cause, whichever comes first;
- Transplantation rate is the percentage of subjects undergoing allogeneic HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens);
- Subject reported QoL and symptoms as assessed with the EORTC QLQ-C30 Questionnaire;
- General health status assessed using EuroQol (EQ-5D-5L) Questionnaire;

	• Healthcare resource utilization. **Pharmacokinetics** • PK concentration for quizartinib and its metabolite (AC886) and PopPK analysis results. • For PK-ECG-Biomarker Substudy: PK concentrations and PK parameters (area under the concentration versus time curve [ng•h/mL] from the time 0 to 24 hours [AUC_{0-24}], maximum plasma concentration [Cmax], minimum plasma concentration [Cmin], and time to maximum plasma concentration [Tmax]) for quizartinib and AC886; **Pharmacodynamic** • FLT3-ITD autophosphorylation activity in an ex vivo plasma inhibitory activity (PIA) assay. **Biomarker** • FLT3-ITD MRD (results will not be available until the end of the study). • Mutations in the kinase and juxtamembrane domains of FLT3-ITD and other mutations known to be associated with AML or myeloid diseases (eg, CEBPA, DNMT3A, IDH1, IDH2, Kit, NPM1, and NRAS), determined with bone marrow or whole blood samples.
Planned Sample Size:	The target sample size will be approximately 536 subjects, randomized in a 1:1 ratio to receive quizartinib/placebo: administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles.
Statistical Analyses:	**Efficacy Analyses** Efficacy analyses will be performed on the Intent-to-treat (ITT) Analysis Set and Per-protocol Analysis Set. All other efficacy exploratory analyses will be performed based on ITT Analysis Set and availability of assessment. The efficacy analyses will be performed according to the treatment groups assigned at Randomization. Overall survival is the primary efficacy endpoint for this study. Comparison of distribution of OS between treatment groups will be made using a stratified log-rank test with the 3 stratification factors used in randomization at a 2-sided 5% significance level. The median OS will be calculated based on Kaplan-Meier

estimates and the corresponding 95% confidence interval (CI) will be calculated using the method provided by Brookmeyer and Crowley.

The OS analysis will be performed:

- When the target 287 OS events are observed and a minimum of 24 months has elapsed since the last subject was randomized.
- If the target 287 OS events are not achieved by 24 months since the last subject was randomized, then the analysis will be performed at a maximum of 30 months after the last subject is randomized.

For the secondary analyses, comparison of distribution of EFS between the 2 treatment groups will be made using a stratified log-rank test with the 3 stratification factors used in randomization. The distribution function of EFS will be estimated using the Kaplan-Meier method. EFS will be analyzed based on the response assessment by the Independent Review Committee (IRC). EFS will also be analyzed based on the investigator's response assessment as one of the sensitivity analyses to be performed.

Comparisons of CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity between treatment groups will be made using a Cochran-Mantel-Haenszel test with the 3 stratification factors used in randomization.

To control for the family-wise type I error rate for the primary and secondary efficacy endpoints, a serial hierarchically ordered gatekeeping strategy will be employed. The primary assessment of OS in the ITT Analysis Set will be evaluated first, and if significant at a 2-sided alpha of 0.05, a statistical evaluation of EFS by IRC, based on the EFS definition in the Guidances,[63,72] will be performed in the ITT Analysis Set. After EFS evaluation, the order of other secondary endpoints to be tested will be CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity. Testing will stop once 1 test in the sequence fails to be statistically significant.

Exploratory efficacy analyses of RFS will be analyzed using the Kaplan-Meier method for subjects achieving CRc.

RFS in subjects who enter the Continuation Phase will be summarized similarly as RFS.

Duration of CR will be analyzed similarly as RFS.

Rate of allogeneic HSCT, rate of CR at end of first Induction cycle, rate of CRc at end of first Induction cycle, rate of CRh after Induction, and rate of MLFS after Induction will be analyzed and CI will be provided.

Pharmacokinetic Analyses

For the PK-ECG-Biomarker Substudy: PK parameters of quizartinib and its metabolite (AC886) will be estimated for subjects who have sufficient plasma concentrations available. Standard non-compartmental analysis will be estimated for subjects with sufficient intense PK data available for the following PK parameters: $AUC_{0\text{-}24}$, Cmax, Cmin, Tmax, and accumulation ratio and parent/metabolite ratio at Day 8 and Day 21 during Cycle 1 of Induction.

Plasma concentrations and PK parameters will be summarized using descriptive statistics by treatment group and by treatment phase when appropriate.

Population PK modeling will be performed for quizartinib and its metabolite (AC886) and details will be provided in a separate PopPK report.

Pharmacodynamic Analyses

A subject is said to have achieved full inhibition at a certain PIA assessment visit if the corresponding PIA value is >90%. Number and percentage of subjects achieving full inhibition will be provided for the quizartinib group. Summary statistics will be provided for the quizartinib group in the Pharmacodynamic Analysis Set.

Biomarker Analyses

Number and percentage of subjects expressing different AML associated mutations will be summarized by treatment groups.

FLT3-ITD allelic ratio will be summarized and presented by treatment groups.

Safety Analyses

Safety analysis will be performed using the Safety Analysis Set. For safety analyses, subjects will be analyzed according to actual treatment received. Safety analyses include frequency and severity of treatment-emergent adverse events (TEAEs).

Adverse events to be included in summary tables will be restricted to TEAEs.

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment group including end of treatment visit as well as for the maximum and minimum post-baseline values.

Abnormal clinical laboratory results will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, if applicable. A shift table, presenting by treatment group the 2-way frequency tabulation for baseline and the worst post-baseline value according to the CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment group including end of treatment visit as well as for the maximum and minimum post-baseline values.

Electrocardiogram parameters will be summarized using descriptive statistics for actual values and for changes from baseline by treatment group by scheduled time of evaluation including end of treatment visit as well as for the maximum post-baseline values. QTcF will be considered as the primary correction method to assess QT corrected (QTc) interval.

The number and percentage of subjects with QT/QTc interval values meeting the criteria will be tabulated (eg, QTcF ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) and QTcF maximum changes from baseline (>30 and >60 ms) over all posttreatment evaluations will be summarized. Electrocardiogram data will also be presented in the data listings. Unless otherwise stated, baseline will be the last measurement before first dose of quizartinib/placebo.

Physical examination findings will be listed for the Safety Analysis Set.

Blood transfusion data will be summarized by treatment group and treatment phases.

Concomitant medications will be coded using the World Health Organization drug dictionary (most recent version). Number and percentage of subjects taking concomitant medications will

	be summarized by ATC2 class and preferred term and presented by treatment group. Subgroup analyses of AEs will be performed if appropriate using subgroups defined in the Statistical Analysis Plan (SAP). **Health Economics and Outcome Research** The patient-reported outcomes (EORTC QLQ-C30, EQ-5D) and the health resource utilization data will be assessed based on a separate analysis plan. The plan will provide details of the descriptive and comparative statistical analyses.

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ABBREVIATION	DEFINITION
ΔQTcF	Change from baseline in QTcF
AE	Adverse event
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil counts
APL	Acute promyelocytic leukemia
AST	Aspartate transaminase
ATRA	All-trans retinoic acid
AUC	Area under the concentration versus time curve (ng•h/mL)
AUC_{0-24}	Area under the concentration versus time curve (ng•h/mL) from the time 0 to 24 hours
AUC_{0-inf}	Area under the concentration-versus-time curve (ng•h/mL) from the time of dosing extrapolated to infinity, calculated as: AUC0-inf = AUClast + Clast/λz
BSA	Body surface area
CI	Confidence interval
Cmax	Maximum plasma concentrations
Cmin	Minimum plasma concentration
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with either incomplete neutrophil or platelet recovery
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome P450
DISS	Drug-induced sweet's syndrome
DLI	Donor lymphocyte infusion
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

ABBREVIATION	DEFINITION
EDC	Electronic data capture
EFS	Event-free survival
EIU	Exposure in utero
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-5L	Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
FSH	Follicle stimulating hormone
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GVHD	Graft-versus-host disease
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
IRB	Institutional Review Board
IRC	Independent Review Committee
ITD	Internal tandem duplication
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IXRS	Interactive web/voice response system
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state

ABBREVIATION	DEFINITION
MRD	Minimal or measurable residual disease
ms	Millisecond
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall survival
P-gp	P-glycoprotein
PIA	Plasma inhibitory activity
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PPS	Per-protocol analysis set
PRO	Patient-reported outcome
QLQ-C30	Core quality of life questionnaire
QoL	Quality of life
QTc	QT interval corrected
QTcF	QT interval corrected with Fridericia's formula
RFS	Relapse-free survival
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total serum bilirubin
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Background

1.1.1. Investigational Product

1.1.1.1. Name

Quizartinib

1.1.1.2. Description

Quizartinib is a Class III receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective inhibition of FMS-like tyrosine kinase 3 (FLT3). Quizartinib is currently being studied as a treatment for acute myeloid leukemia (AML).

1.1.1.3. Intended use under investigation

Quizartinib in combination with anthracycline and cytarabine chemotherapy is being investigated as treatment for newly diagnosed AML patients with FLT3 internal tandem duplication (ITD) mutations.

1.1.1.4. Nonclinical studies

Please refer to the current Quizartinib Investigator's Brochure (IB) for nonclinical data supporting its use in clinical studies.[2]

1.1.1.5. Clinical Experience

Quizartinib is currently being studied as a treatment for AML. There is an ongoing global, Phase 3, open-label study of quizartinib monotherapy versus salvage chemotherapy in AML subjects with FLT3-ITD mutations who are refractory or relapsed in 6 months with or without hematopoietic stem cell transplantation (HSCT) Consolidation (QuANTUM-R). The study is currently enrolling patients and the data from the study are not available.[2]

CCI [redacted] A brief summary of previous studies is given below. Please refer to the most recent IB for additional information.[2]

In the first in human Phase 1 study, CP0001, quizartinib was administered with intermittent dosing (14 days on drug followed by 14 days rest) from 12 mg to 450 mg and continuous dosing at 200 mg and 300 mg for 28 days in 76 subjects with relapsed/refractory AML, regardless of FLT3-ITD mutation status.[3] Plasma taken from subjects and assayed in an in vitro plasma inhibitory activity (PIA) assay showed rapid and durable inhibition of FLT3-ITD phosphorylation as early as 2 hours after the first dose. The overall response rate was 53% in FLT3-ITD (+) subjects and 14% in FLT3-ITD (-) subjects.[3]

The response rate observed in Study CP0001 was confirmed in the Phase 2 study, AC220-002, of single agent quizartinib in relapsed or refractory AML. In this Phase 2 study a total of 333 subjects were enrolled in 2 cohorts; Cohort 1 included subjects 60 years or older who were relapsed or refractory to 1 line of therapy and Cohort 2 included subjects 18 years or older who

were relapsed or refractory to salvage therapy or relapsed after HSCT. In Cohort 1, the composite complete remission (CRc) rate was 57% in FLT3-ITD (+) subjects with a median survival of 25.3 weeks.[2,4] Cohort 2 showed a CRc rate of 46% in FLT3-ITD (+) subjects with a median survival of 24.0 weeks.[2] Importantly, 35% of Cohort 2 FLT3-ITD (+) subjects were bridged to HSCT.[5]

The maximum tolerated dose (MTD) determined in the Phase 1 study, CP0001, was 200 mg continuous daily dosing.[3] However, in the Phase 2 Study (AC220-002) 35% of subjects experienced Grade 3 QT prolongation at the 200 mg dose and therefore the dose was reduced. A single case of Grade 4 QT prolongation, Torsades de Pointes, was reported in the AC220-002 Study in a subject with pneumonia, atrial fibrillation, taking concomitant medications known to cause QT prolongation.[6] No deaths related to QT prolongation have been reported.[2]

A Phase 2b Study (2689-CL-2004) was subsequently conducted, which enrolled 76 subjects with FLT3-ITD (+) AML randomized to 60 mg or 30 mg daily, to examine efficacy and toxicity at these lower doses. Both males and females were randomized at each dose. The study showed that the CRc rate was similar at both lower doses and to that observed in the earlier Study AC220-002 (Table 1.1).[7] QT prolongation was dose-dependent and was substantially reduced at the lower doses (Table 1.2).

Table 1.1: Summary of the Efficacy Findings Across all 5 Daily Doses Studied in the Phase 2 Program

Study	**2689-CL-2004**		**AC220-002**		
Quizartinib Dose	**30 mg (N=38)**	**60 mg (N=38)**	**90 mg (N=57)**	**135 mg (N=67)**	**200mg (N=12)**
CRc rate	47%	47%	47%	45%	42%
Partial Remission rate	13%	24%	25%	28%	50%

CR=complete remission; CRc=composite complete remission (CR+CRp+CRi); CRi=CR with incomplete neutrophil recovery; CRp=CR with incomplete platelet recovery
Source: Russell N, Tallman MS, Goldberg S, et al. Abstract 187 (Table 8)[7]

Table 1.2: Summary of the QTcF Findings Across all 5 Daily Doses Studied in the Phase 2 Program

Study	2689-CL-2004		AC220-002		
Quizartinib Dose	30 mg (N=38)	60 mg (N=36)[a]	90 mg (N=57)	135 mg (N=67)	200 mg (N=12)
Maximum value of QTcF (ms)					
>480 to ≤500 (Grade 2)	5%	14%	21%	13%	33%
>500 (Grade 3)	5%	3%	21%	15%	42%
Maximum change in QTcF from baseline (ms)					
≤30	50%	44%	9%	9%	0%
>30 to ≤60	47%	36%	46%	51%	8%
>60	5%	19%	46%	39%	92%

QTcF=QT interval corrected with Fridericia's formula
[a] Two subjects in the 60 mg/day group were randomized but never treated with quizartinib
Source: Schiller G, Tallman MS, Goldberg S, et al[8]

Common adverse events (AEs) observed in the Phase 1 and 2 studies included gastrointestinal disorders (nausea, diarrhea, and vomiting), hematologic disorders (anemia, neutropenia, and thrombocytopenia), febrile neutropenia, fatigue, and QT prolongation. Although hematologic toxicity is associated with underlying disease, safety reports from Study AC220-002 in AML indicate delayed recovery or continued suppression of absolute neutrophil counts (ANC) and platelets as a consequence of continued treatment with quizartinib.[2]

1.1.1.5.1. Clinical Pharmacology

The tablet formulation, which will be used in Phase 3 studies, exhibited comparable relative bioavailability to the solution formulation which was administered in the earlier Phase 1 and 2 studies. In a relative bioavailability study (AC220-014) in fasting, healthy volunteers and oral administration of a single 60 mg dose (2x30 mg tablets) of quizartinib, the median time to maximum plasma concentration (Tmax) was 4 (minimum, 2; maximum; 8) hours for quizartinib and 8 (minimum, 4; maximum; 48) hours for AC886 (the major active metabolite of quizartinib, with similar potency to the parent molecule, quizartinib). The geometric mean (coefficient of variation [CV] %) terminal half-life was 64.9 (75%) hours and 53.5 (40%) hours for quizartinib and AC886, respectively. Quizartinib and AC886 showed dose-proportional increases in area under the concentration versus time curve (ng•h/mL) (AUC) and maximum plasma concentrations (Cmax) over the tested dose range of 30 to 90 mg.[2]

Following a single-oral dose of [^{14}C]-quizartinib, 76.3% of total radioactivity was recovered in feces with only 1.6% recovered in urine 14 days after dosing (AC220-006). Excretion of radioactivity was still ongoing at study completion at Day 14, mainly in feces. AC886 was the only major circulating metabolite and is formed by cytochrome P450 (CYP3A4).[2]

In a Phase 2b study, 2689-CL-2004, in which AML subjects receiving multiple doses of quizartinib at 30 mg/day or 60 mg/day, steady-state was reached by Day 15 for both quizartinib and AC886, consistent with the terminal half-life of approximately 3 days observed in healthy

subjects. Geometric means (CV%) of the metabolite to parent ratios (Area under the concentration versus time curve (ng•h/mL) from the time 0 to 24 hours [AUC_{0-24}]) were 0.40 (124%) and 0.35 (91.0%) for 30 mg/day and 60 mg/day, respectively, on Day 1 and were 0.52 (123%) and 0.54 (138%) for 30 mg/day and 60 mg/day, respectively, on Day 15.

Previous analysis evaluated QT interval corrected with Fridericia's formula (QTcF) prolongation (change from baseline in QTcF [ΔQTcF]) and concentration relationship with pharmacokinetics (PK) and electrocardiogram (ECG) data collected [redacted] An updated analysis was performed by incorporating circadian rhythm using a non-linear mixed effect model. The covariates evaluated were quizartinib and AC886 plasma concentrations and sex. QTcF changes with circadian rhythm and is linearly dependent on quizartinib plasma concentrations. AC886 plasma concentrations and sex are not significant covariates for the QTcF prolongation. This updated model was used to predict QTcF prolongation at steady state geometric mean Cmax normalized to [redacted]

A drug-drug interaction study assessing the effect of strong and moderate CYP3A4 inhibitors on quizartinib PK showed [redacted] Additionally, concomitant ketoconazole and concomitant fluconazole resulted in an increase in predicted quizartinib Cmax at steady state after repeat daily dosing, approximately [redacted]

A drug-drug interaction (DDI) study was conducted [redacted] quizartinib [redacted] or lansoprazole [redacted] administered once daily for 5 days with a single dose of quizartinib [redacted] administered on Day 5. A weak PK drug-drug interaction was observed between quizartinib and lansoprazole. [redacted] However, the decrease in quizartinib exposure is not considered to be clinically significant. Other types of gastric pH modifiers (eg, antacids and H2 antagonists) are also not expected to have a clinically significant DDI with quizartinib.

A food-effect study involving single-dose administration of a [redacted] quizartinib to healthy volunteers under fasting conditions or with a high-fat meal indicated that AUC was increased by approximately [redacted] of the Cmax ratio of fed to fasting condition was contained within the [redacted] interval. This increase in exposure is not clinically significant, and therefore quizartinib can be taken with or without food. However, food did prolong the time to peak concentrations, time to maximum plasma concentration [redacted]

1.1.1.5.2. Combination Studies with Induction Chemotherapy

Study 2689-CL-0005 is a Phase 1, open-label, multiple-dose, dose-escalation study in patients with newly diagnosed AML [FLT3-ITD (+) or FLT3-ITD (-)]. The treatment and follow up phases of the study has been completed.

The dose escalation was conducted using a modified 3+3 design, where 6 subjects were enrolled at each dose level. The subjects were given cytarabine 200 mg/m^2 × 7 days and daunorubicin 60 mg/m^2 × 3 days (7+3) for Induction and high dose intermittent cytarabine 3 g/m^2 every 12 hours on Days 1, 3, and 5 for Consolidation. Quizartinib was administered daily for either 7 or 14 days, starting at Day 4 of induction and/or consolidation chemotherapy. Subjects were allowed to proceed directly to a stem cell transplant after achieving a response or receive further quizartinib as maintenance therapy after Consolidation if they were not transplant eligible. Three dose levels were tested; 60 mg × 7 days, 60 mg × 14 days, and 40 mg × 14 days. Through May 31, 2013 18 subjects were enrolled in the study. The median age of subjects was 43 years (minimum, 22; maximum, 60). Of the 18 subjects, 16 had the FLT-ITD mutation. At 60 mg × 7 days, one of the 6 subjects had a dose limiting toxicity (DLT, grade 3 hyponatremia). At 60 mg × 14 days, 2 of the 6 subjects had a DLT (Grade 3 QT corrected [QTc] prolongation and Grade 4 pericarditis) which exceeded the pre-specified criteria so 40 mg × 14 days was then explored. At 40 mg × 14 days, 1 of the 6 subjects had a DLT (Grade 3 constrictive pericarditis). The most common (20%) treatment-related AEs were nausea (42%), diarrhea (32%), anemia (26%), febrile neutropenia (26%), neutropenia (21%), fatigue (21%), pyrexia (21%) and thrombocytopenia (21%). The most common (10%) Grade 3 or 4 treatment-related AEs were febrile neutropenia (26%), thrombocytopenia (21%) anemia (21%), neutropenia (21%), leucopenia (16%), and nausea (11%). The maximum tolerated dose was identified as 40 mg for 14 days or 60 mg for 7 days.[2,9]

The AML18 pilot quizartinib dose-escalation study was an investigator-sponsored study conducted in the UK that enrolled newly diagnosed (FLT3 [+] and FLT3 [-]) AML patients greater than 60 years old.[1] Quizartinib was administered with standard chemotherapy comprised daunorubicin, cytarabine, and etoposide.[10]

Six cohorts with escalating doses of quizartinib (60 mg, 90 mg or 135 mg based on doses used in the Phase 2 AC220-002 study with quizartinib) for 7 or 14 days were planned. If 60 mg was not tolerated dose de-escalation to 40mg for 7 or 14 days was allowed. Because of the presumed increased sensitivity in females to QTc prolongation, each cohort required a minimum of 3 females. The day of safety evaluation was on completion of the chemotherapy in course 2.

Fifty-five subjects with a median age of 69 years (minimum, 62; maximum, 87) were enrolled, of whom 48 were evaluable. Four subjects were FLT3-ITD (+). Thirteen subjects (4 males, 9 females) entered Cohort 1 (60 mg for 7 days). No DLTs were seen in males but 3 DLTs occurred in females (all grade 4:1 cardiac (myocardial infarction), 1 hypokalemia; 1 mucositis) so this cohort exceeded tolerability for females. 8 subjects (all males) entered Cohort 2 (60 mg for 14 days) where 4 DLTs (all grade 3; 3 QTc prolongation, 1 appetite loss) were seen, so this cohort exceeded tolerability for males.[10] In the 40 mg for 14 day cohort, there was 1 DLT (hematological) of 5 evaluable males and 0 of 8 evaluable females had a DLT.

Induction death (death within 30 days) occurred in 3/46 (6.5%) evaluable patients. Complete remission (CR) was achieved in 33/42 (79%; including all 4 FLT3-ITD [+]) of subjects evaluable

for CR. Overall median time to neutrophil and platelet count recovery (neutrophils to 1000/mm^3; platelets to 100,000/mm^3) was prompt (28 and 22 days post Course 1; 22 and 19 days post Course 2, respectively). No subjects received stem cell transplantation.

Based on data from these 2 clinical studies, quizartinib is predicted to be tolerated and provide sufficient clinical benefit administered in subjects as 40 mg dose once daily for 14 days.

1.1.1.5.3. Maintenance Study: 2689-CL-0011 in AML

Allogeneic transplant has become an accepted standard of care for consolidating newly diagnosed FLT3-ITD AML subjects in first remission.[10, 11, 12] An ongoing Phase 1 study of quizartinib as maintenance therapy in subjects with AML who have been treated with an allogeneic HSCT (2689-CL-0011) has enrolled 13 subjects with AML in morphologic remission (<5% bone marrow blasts) during first or second remission following an allogeneic HSCT.[1] These subjects were identified as FLT3-ITD (+) at diagnosis, and after recovery of blood counts post-HSCT were treated with doses of 40 mg/day (n=7) and 60 mg/day (n=6) of quizartinib.[13]

Preliminary data has shown that both doses are well tolerated and the median number of cycles administered was 18.[12] One patient relapsed on study drug (Cycle 1). One patient had Grade 2 graft-versus-host disease (GVHD) on quizartinib. There was no Grade 3 QTcF prolongation. Preliminary results showed that all 13 subjects had experienced at least 1 treatment-emergent AE (TEAE); diarrhea (62%), fatigue (54%), nausea (54%), vomiting (54%), GVHD in skin (38%), neutropenia (38%), anemia (31%), dry eye (31%), dysgeusia (31%), peripheral edema (31%), pyrexia (31%), and upper respiratory tract infection (31%) were reported in more than 3 subjects each. Three subjects discontinued treatment due to AEs: Grade 4 possibly-related neutropenia; Grade 3 not related hemolytic anemia; and Grade 2 possibly related corneal epithelium defect.[2,13] Per study protocol, further dose escalation to 90 mg/day was allowed but based on data from the 2689-CL-2004 study examining 30 mg and 60 mg/day doses and showing a high level of clinical activity with reduced QT prolongation compared to higher doses, it was decided that no further dose escalation was desirable.[8] These data indicate that quizartinib can be safely administered as maintenance therapy after HSCT with promising early efficacy data.

1.2. Study Rationale

FLT3 is a transmembrane tyrosine kinase that belongs to the Class III split-kinase domain family of RTKs. FLT3 is expressed in AML cells in approximately 90% of patients and stimulates survival and proliferation of leukemic blasts.[14, 15] Moreover, FLT3 is mutated in 30% of AML cases.[16, 17] The 2 types of mutations found in AML include ITDs (24%) and point mutations in the activation loop (approximately 7%).[2, 16] Patients with FLT3-ITD mutations have a worse prognosis when treated with conventional chemotherapy compared with patients with wild-type FLT3 due to a higher relapse rate.[18] No FLT3 inhibitors have been approved for AML due to limited clinical utility with lack of durable responses when administered as single agents.[19, 20] Initial studies with the next generation quizartinib are encouraging based on a high response rate when administered as monotherapy. However acute myeloid leukemia is a polyclonal disease and patients with FLT3-ITD mutated AML may experience greater clinical benefit when quizartinib is administered in combination with standard chemotherapy.[17] In addition to FLT3, quizartinib inhibits c-KIT stem cell factor CD117 which is expressed in more than 70% of AML. Furthermore, KIT mutations occur in more than 40% of core binding factor leukemias.[21] In

addition, KIT mutations are evident in Runt-related transcription factor 1/ runt-related transcription factor 1; translocated to, 1-(+) AML.[22, 23]

Results from the Phase 1 2689-CL-0005 and AML18 studies of quizartinib in combination with standard induction and/or consolidation therapy for subjects with newly diagnosed FLT3-ITD (+) AML showed that quizartinib at the doses of 40 mg for 14 days can be safely administered with induction and/or consolidation chemotherapy. In addition, the majority of FLT3-ITD (+) subjects achieved CR. The data from Study 2689-CL-0011 indicate that quizartinib can be safely administered as maintenance after HSCT with promising early efficacy data with only 1 of 13 FLT3-ITD (+) patients experiencing disease relapse.[13] These findings serve as the basis for studying combination of quizartinib with chemotherapy and subsequent continuation treatment following consolidation chemotherapy or HSCT in subjects with newly diagnosed AML with FLT3-ITD mutations.

1.2.1. Selection of ≥3% FLT3-ITD Allelic Ratio as Cutoff for Study Eligibility

In previous Phase 2 studies with quizartinib, subjects with an allelic ratio of FLT3-ITD to total FLT3 of >10% were defined as ITD(+). Analysis of "ITD(-)" subjects from Study AC220-002 showed that those subjects with a low level (≤10%) of the ITD mutation had similar response rates to positive (>10%) subjects, while those with no detectable ITD mutation (<0.3%) had lower response rates. Therefore, for the ongoing QuANTUM-R Phase 3 study of relapsed and refractory AML subjects and for this QuANTUM-First study the cutoff will be reduced to ≥3% based on the limit of quantitation for the clinical diagnostic assay. The lower ITD ratio for eligibility will allow those subjects with a reliably detectable and quantifiable ITD mutation to be enrolled and to determine the potential benefit from quizartinib.

1.2.2. Selection of Chemotherapy Regimens

The National Comprehensive Cancer Network (NCCN) Guidelines (Version 1.2015) for induction chemotherapy for AML include a 3-day administration of an anthracycline (idarubicin 12 mg/m^2 or daunorubicin 45 mg /m^2 to 90 mg /m^2) plus 7 days of standard dose cytarabine (cytosine arabinoside) ("7+3" chemotherapy regimen).[24, 25, 26]

Anthracycline (idarubicin 12 mg/m^2 or daunorubicin 45 mg /m^2 to 90 mg /m^2) is administered as a short intravenous (IV) infusion or bolus daily for 3 days (Days 1 to 3). The dose of cytarabine is usually 100 mg/m^2 to 200 mg/m^2, administered as a continuous IV infusion daily for 7 days (Days 1 to 7).[24]

Depending on age and patient selection about 70 to 80 percent of patients achieve a CR with idarubicin or daunorubicin based induction therapy.[27, 28] Most remissions come after a single course. Until recently, daunorubicin had been commonly administered at a dose of 45 mg/m^2; however, randomized studies suggest that higher doses of daunorubicin (eg, 60 mg/m^2 to 90 mg/m^2 per day) are more effective and no more toxic than 45 mg/m^2. A Phase 3 trial of 657 adults (17 to 60 years old) with untreated AML randomly assigned induction therapy with 7 days of continuous IV infusion cytarabine (100 mg/m^2 per day) plus 3 once-daily doses of daunorubicin at 45 mg/m^2 or 90 mg/m^2. Compared to the 45 mg/m^2 daunorubicin dose, patients assigned to the 90 mg/m^2 dose had a higher CR rate (71% versus 57 %), a longer median overall survival (OS), 24 versus 16 months) and similar rates of severe (grade 3/4/5) AEs.[28] A similar

randomized trial in older adults (>60 years) also reported higher CR rates with 90 mg/m^2 daunorubicin compared with 45mg/m^2 (52% versus 35%).[29]

However, in another trial (AML17), 1206 adults with untreated AML or high-risk myelodysplastic syndrome were randomly assigned induction therapy with cytarabine (100 mg/m^2 every 12 hours on Days 1 to 10 inclusive) plus daunorubicin at a dose of either 90 mg/m^2 or 60 mg/m^2 on Days 1, 3, and 5.[25] All patients received a second Induction course that included daunorubicin 50 mg/m^2 on days 1, 3, and 5. There was no overall difference in CR rate. The 60 day mortality was increased in the 90 mg/m^2 arm (10% versus 5%), which resulted in no difference in overall 2 year survival (59% versus 60%).[25]

The proposed Induction regimen for QuANTUM-First is the standard "7+3" regimen with the choice of daunorubicin 60 mg/m^2 or idarubicin 12 mg/m^2 on Days 1 to 3 combined with cytarabine 100 mg/m^2 (200 mg/m^2 if institutional or local standard) on Days 1 to 7.

The NCCN Guidelines (Version 1.2015) for post-remission chemotherapy for AML include consolidation with high-dose cytarabine. The NCCN recommended high dose cytarabine is 2 to 3 g/m^2 (1 to 1.5 g/m^2 for subjects ≥60 years of age) administered as an IV infusion every 12 hours on Days 1, 3, and 5 for a total of 6 doses.[24] European Leukemia Net recommendations suggest using high dose cytarabine as a consolidation therapy in clinical trials only.[30]

However, there is no clear consensus recommendation for a Consolidation cytarabine regimen for FLT3 (+) patients. The NCCN recommends enrolling FLT3 (+) patients into a clinical trial.[24] European LeukemiaNet recommendations suggest to use HSCT as a consolidation for patients with FLT3-ITD who are 18-60 years old and to use "modest" dose of cytarabine for consolidation in patients over age of 60.[30]

The proposed consolidation regimen for QuANTUM-First is cytarabine 3 g/m^2 twice daily for subjects <60 years old and 1.5 g/m^2 twice daily for subjects ≥60 years old and on Days 1, 3, and 5. The dose of cytarabine has been defined as 3 g/m^2 based on data from the CALGB study in which cytarabine doses of 100 mg/m^2 or 400 mg/m^2 for 5 days or 3 g/m^2 twice daily on Days 1, 3, and 5 were compared.[31] The 3 g/m^2 dose was found to have superior disease free survival compared to the lower doses.[31]

1.2.3. Rationale for Quizartinib Dose Selection

During the Induction Phase and Consolidation Phase subjects will receive quizartinib 40 mg or matching placebo, once daily for 14 days per cycle, immediately following standard chemotherapy. The 40 mg dose was selected based on the results of Study 2689-CL-0005 and the investigator initiated AML18 pilot study. In these studies quizartinib 40 mg × 14 days was identified as the MTD, when given in addition to standard chemotherapy in newly diagnosed AML subjects older than 60 years.

In addition to the clinical data, the quizartinib dose of 40 mg following chemotherapy is supported by data from pharmacodynamic assays. The in vitro PIA measures the ability of plasma taken at various times before and after dosing with quizartinib to inhibit signaling in FLT3-ITD (+) cell lines. The inhibitory activity demonstrated in this assay has been found to correlate with clinical response to different FLT3 inhibitors.[19] Plasma inhibitory activity data from the Phase 2b (2689-CL-2004) studies demonstrated that 30 mg is the minimum dose for complete and rapid inhibition of FLT3-ITD signaling in this assay.[32] However, there are several

compensatory mechanisms, such as increases in FLT ligand and direct cell to cell contact between blast cells and stromal cells that reduce the effectiveness of FLT3 inhibitors and protect leukemic blasts from apoptosis.[33, 34] Therefore it is important to administer a dose above the minimum to ensure complete and durable inhibition of the target, particularly when quizartinib is administered for only 14 days and not continuously as with monotherapy studies.

Data from Study AC220-015, which examined the effect of strong and moderate CYP3A4 inhibitors on quizartinib PK in human volunteers, indicate that concomitant ketoconazole, a strong CYP3A4 inhibitor, will increase $AUC_{0\text{-inf}}$ approximately 2-fold, and concomitant fluconazole, a moderate CYP3A4 inhibitor, will increase quizartinib $AUC_{0\text{-inf}}$ approximately 1.2-fold.[2] Additionally, predicted quizartinib Cmax at steady state after repeat daily dosing will increase approximately 2.0-fold and 1.2-fold, respectively, with concomitant ketoconazole and fluconazole. Subjects who begin treatment with a strong CYP3A4 inhibitor while receiving quizartinib will be required to be reduced from 40 mg/day to 20 mg/day. If the strong CYP3A4 inhibitor is discontinued, the dose of quizartinib can be resumed at the regularly scheduled dose. No dose reduction of quizartinib is required when subjects are coadministered a moderate or weak CYP3A4 inhibitor. If quizartinib/placebo is interrupted, missed doses will not be made up.

Quizartinib has been shown to be a P-glycoprotein (P-gp) substrate based on in vitro studies. However, clinical data suggest that P-gp plays a minimal role in the absorption or clearance of quizartinib. Based on the mass balance study, quizartinib appears to be highly absorbed into enterocytes and has minimal renal excretion (AC220-006). Inhibition of P-gp/CYP3A4 by ketoconazole resulted in a small change (eg, <20%) in absorption of quizartinib (AC220-015). Therefore no dose adjustment is required when quizartinib is coadministered with a P-gp inhibitor.

The potential of quizartinib and AC886 to inhibit cytarabine metabolism was examined in human liver S9. Pooled human liver S9 was incubated with cytarabine (50 μM) in the presence of 6 concentrations of quizartinib or AC886 (0.1, 0.3, 1, 3, 10, and 30 μM) for 15 minutes at 37°C. At the end of the incubation period the reactions were terminated and samples were analyzed for ara-U, a metabolite of cytarabine. Gemcitabine was used as a positive control inhibitor of cytarabine metabolism by cytidine deaminase. Based on these data, quizartinib does not inhibit cytarabine metabolism (up to 30 μM for parent and metabolite).

The quizartinib concentration relationship to QTcF prolongation (ΔQTcF) was evaluated by incorporating circadian rhythm with PK and ECG data collected from Study 2689-CL-2004 into a non-linear mixed effect model. The covariates evaluated were quizartinib and AC886 plasma concentrations and sex. QTcF changes with circadian rhythm and is linearly dependent on quizartinib plasma concentrations. AC886 plasma concentrations and sex are not significant covariates for the QTcF prolongation. This model was used to predict QTcF prolongation at steady state geometric mean Cmax normalized to 40 mg. The analysis predicted that administration of 40 mg/day quizartinib with dose reduction to 20 mg/day for the subjects on strong CYP3A4 inhibitors resulted in the upper 90% CI of ΔQTcF less than 17 ms. These results suggest that the proposed quizartinib dose regimen has acceptable risk of QT prolongation based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 Guidance stating: “Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic.”[35]

During the Continuation Phase, subjects will receive study drug, quizartinib 30 mg or matching placebo, once daily, starting on Day 1, with no breaks between cycles. Study drug dosage will be increased on Day 16 to 60 mg once daily for subjects where QTcF is maintained ≤450 ms and study drug is tolerated. This escalating dose schedule based on QTcF interval at drug steady-state is the same as that in the ongoing QuANTUM-R Study. The 30 mg and 60 mg doses were chosen, based on the results of Study 2689-CL-2004. In that study quizartinib 30 mg or 60 mg, was given to subjects with FLT3-ITD (+) AML, and 60 mg was identified as the target dose as it showed rapid and durable inhibition of FLT3 phosphorylation on pharmacodynamic assay. Additional dose adjustments for toxicity including myelosuppression and administration of strong CYP3A4 inhibitors from 30 mg/day to 20 mg/day, or 60 mg/day to 30 mg/day, are included. If quizartinib/placebo is interrupted, missed doses will not be made up. Once the dose is increased to 60 mg/day, the subject may continue on this dose as long as dose reduction is not needed.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of overall survival (OS) in subjects with newly diagnosed AML with FLT3-ITD mutations.

2.1.2. Secondary Objectives

The secondary objectives are to:

- Compare the following in subjects treated with quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles):
  - Event-free survival (EFS)
  - Composite complete remission rate (CRc = CR + CR with incomplete neutrophil or platelet recovery [CRi]) after Induction;
  - Percentage of subjects achieving CRc with FLT3-ITD minimal or measurable residual disease (MRD) negativity after Induction;
  - Complete remission (CR) rate after Induction;
  - Percentage of subjects achieving CR with FLT3-ITD MRD negativity after Induction.
- Further characterize the safety profile of quizartinib administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles.
- Assess the pharmacokinetics (PK) of quizartinib and its metabolite (AC886).

2.1.3. Exploratory Objectives

The exploratory objectives are:

To evaluate the following in subjects treated with quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles):

- Relapse-free survival (RFS);
- Duration of CR;
- CR rate at the end of first Induction Cycle;
- CRc rate at the end of first Induction Cycle;

- Rate of CR with partial hematologic recovery (CRh) after Induction (only for Independent Review Committee [IRC] assessment of response);
- Rate of morphologic leukemia-free state (MLFS) after Induction (only for IRC assessment of response);
- RFS in subjects who enter the Continuation Phase, after achieving CRc in Induction;
- Transplantation rate;
- Healthcare resource utilization;
- Impact on subject reported quality of life (QoL) and symptoms, as assessed by European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30);
- Change in general health status measured by EQ-5D-5L.

To assess the population PK (PopPK) of quizartinib and exposure-response relationship for QTcF including assessment of post-anthracycline administration, and clinical response measures;

To assess the pharmacodynamics and biomarkers of quizartinib.

2.2. Study Hypothesis

Quizartinib will prolong OS in subjects ≥18 and ≤75 years old with newly diagnosed AML with FLT3-ITD mutations when administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles.

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, global study to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as continuation therapy for up to 36 cycles) on the primary endpoint of OS in subjects with newly diagnosed AML with FLT3-ITD mutations. The study duration is described in Section 3.1.1.

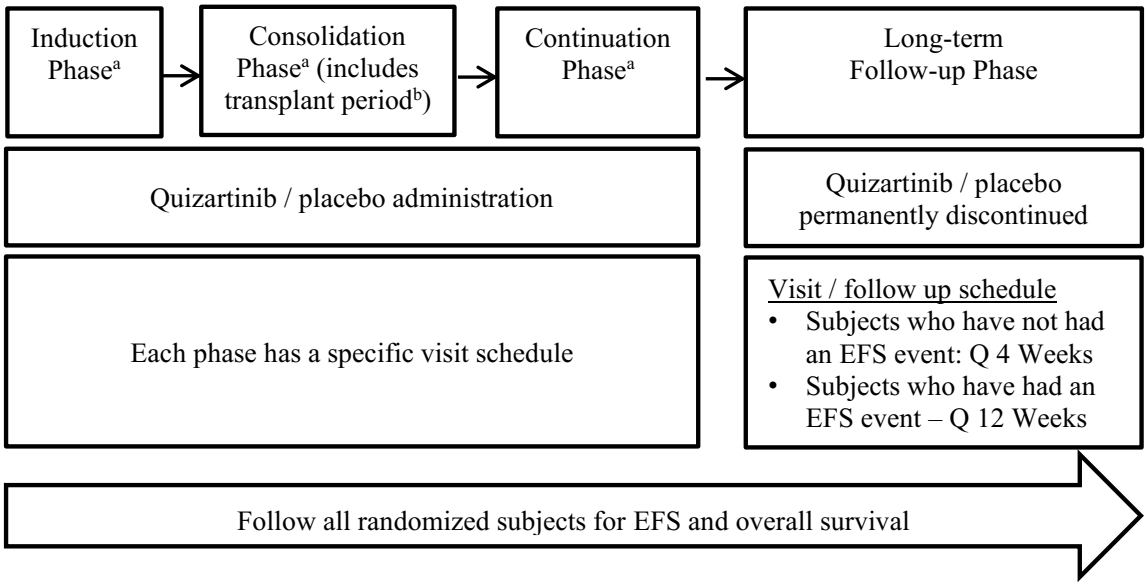
This study will be conducted in approximately 250 study sites worldwide.

The target sample size will be approximately 536 subjects. Randomization will be done in a 1:1 ratio into the 2 treatment groups (quizartinib or placebo). Randomization will be stratified based on:

- Region (North America, Europe, Asia/Other Regions)
- Age (<60 years old, ≥60 years old)
- White blood cell (WBC) count at the time of diagnosis of AML (<40×10^9/L, ≥40×10^9/L)

The study design consists of 4 consecutive phases (Induction, Consolidation, Continuation, Long-Term Follow-up) as outlined in Section 3.2.2 and shown in Figure 3.1. Figure 3.2 shows the study design from Screening into the Treatment Period.

Figure 3.1: Study Summary

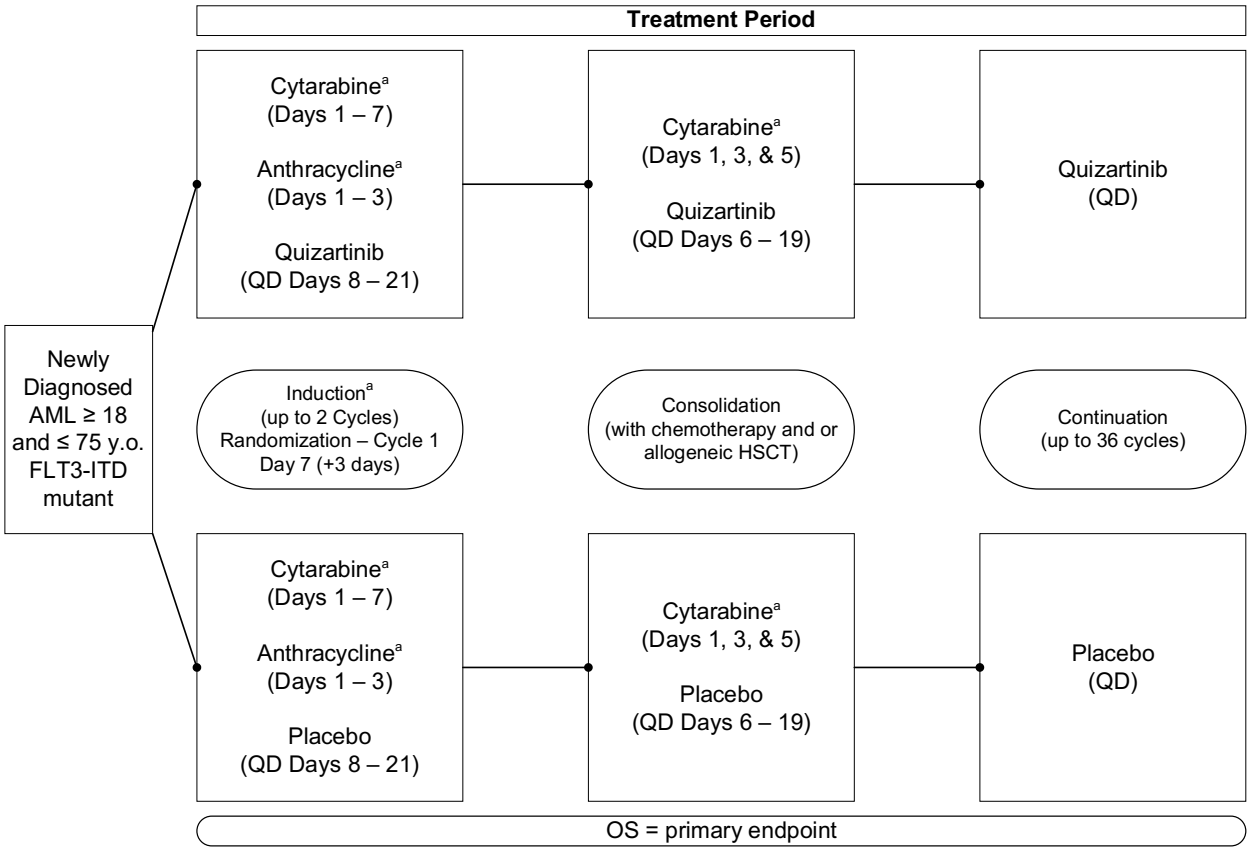


EFS=event-free survival; Q=every

[a] Subjects who permanently discontinue quizartinib/placebo in the Induction, Consolidation, or Continuation Phases will enter the Long-Term Follow-up Phase.

[b] During transplant period, quizartinib/placebo interrupted and subjects followed for relapse and survival status.

Figure 3.2: Study Design Schematic (Screening to Treatment Period)



AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication; OS = overall survival; QD=once a day; y.o. =years old

[a] During Induction Cycle 2 investigators may choose to administer the "7+3" chemotherapy regimen, or the "5+2" chemotherapy regimen, and quizartinib/placebo will therefore start on Day 8 or Day 6, respectively.

3.1.1. Study Duration

The total duration of subject participation will be until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first. Subjects will be followed for EFS and OS events after completion of induction and consolidation therapy, whether or not the subject receives continuation therapy. Close and uniform follow up is essential to determine the timing of relapse in each treatment arm.

The total duration of treatment with quizartinib/placebo will be up to 42 cycles (inclusive of Induction, Consolidation, and Continuation Phases).

The OS analysis will be performed:

- When the target 287 OS events are observed and a minimum of 24 months has elapsed since the last subject was randomized.
- If the target 287 OS events are not achieved by 24 months since the last subject was randomized, then the analysis will be performed at a maximum of 30 months after the last subject is randomized.

All other efficacy analyses will be performed at the same time as the OS analysis.

The **primary completion date** is the date when the final OS analysis (up to a maximum of 30 months after the last subject is randomized) has been completed. All subjects still on treatment and continuing to derive benefit from study drug at the primary completion date will continue to follow the study schedule of assessments until the overall End of Study is reached.

Overall End of Study will occur when:

- all subjects have discontinued treatment and discontinued long-term survival follow-up or have died
- an alternative study becomes available, for subjects continuing to derive benefit from treatment with quizartinib, where the study drug is offered to these subjects
- the study is discontinued by the Sponsor for other reasons (administrative, program-level or class-related)

The subject's EOS is the date of their last study visit/contact.

3.2. Discussion of Study Design

3.2.1. Treatment Groups

Subjects will be randomized to the quizartinib group or placebo group.

3.2.2. Study Phases

In the Induction, Consolidation, and Continuation Phases, each cycle will be 28 days in duration. Additional time is allowed for recovery of blood counts, if needed, in the Induction or Consolidation Phases.

Subjects in remission following the Induction or Consolidation Phases will have their blood counts monitored at least every 4 weeks and will have a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) collected every 12 weeks for the first 48 weeks, followed by every 24 weeks for the next 48 weeks, until relapse or 96 weeks have passed, whichever occurs first. For more details see the bone marrow aspirate specimen collection in Section 6.2.3 and Section 6.4.2.1.1.

3.2.2.1. Induction Phase (up to 2 cycles)

During the Induction Phase subjects will be treated with quizartinib plus the cytarabine and anthracycline regimen or placebo plus the cytarabine and anthracycline regimen. Subjects are permitted to receive up to 2 cycles of induction chemotherapy.

Cycle 1

Subjects will begin the cytarabine and anthracycline regimen on Day 1. Cytarabine will be administered by continuous intravenous (IV) infusion for a total of 7 days, starting on Day 1 and ending on Day 8. The anthracycline will be administered on Days 1, 2, and 3.

Subjects will be randomized on Day 7. If necessary, Randomization may be performed later (eg, Days 8 to 10) to allow time for addressing electrolyte abnormalities, QTcF prolongation, etc.

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing should start following the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to start within 3 days of Randomization if possible. If quizartinib/placebo cannot be started within 3 days of Randomization, please contact the Medical Monitor. If quizartinib/placebo is interrupted, missed doses will not be made up.

On Day 21 (window Day 21 to Day 28), a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected for local and central pathology. If this bone marrow does not provide an accurate assessment of response, the bone marrow procedure will be repeated upon count recovery or Day 56 (±3 days), whichever occurs first. Subjects with ≥ 5% blasts at the end of Cycle 1 may receive a second cycle of Induction, if appropriate. At the investigator's discretion, to allow for blood counts to recover or other reasons, the second Induction cycle may start up to 60 days after Day 1 of the first Induction cycle.

Cycle 2

Subjects will begin the cytarabine and anthracycline regimen on Day 1. It is recommended to wait at least 7 days after the last dose of quizartinib/placebo in Cycle 1 of Induction before starting Cycle 2 of Induction, since quizartinib has a long elimination half-life and there are no data on the safety of administering anthracycline within 7 days following quizartinib administration. For Cycle 2 of Induction, investigators may choose to administer a "7+3" or "5+2" regimen.

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will start following the end of the cytarabine infusion, normally on Cycle 2, Day 8 or Cycle 2, Day 6, depending on the chemotherapy regimen selected by the investigator (ie, "7+3" or "5+2", respectively). If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

On Day 21 (window Day 21 to Day 28), a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected for local and central pathology. If this bone marrow does not provide an accurate assessment of response, the bone marrow procedure will be repeated upon count recovery or Day 56 (± 3 Days), whichever occurs first. Subjects with ≥ 5% blasts at the end of Cycle 1 may receive a second cycle of Induction, if appropriate. At the investigator's discretion, to allow for blood counts to recover or other reasons, the first cycle of Consolidation may start up to 60 days after Day 1 of the last Induction cycle.

See Section 5.4.1 for specific treatment administration requirements during the Induction Phase, and Section 6.2.1, Table 17.1, Table 17.2 and Table 17.3 for all procedures to be done during the Induction Phase.

3.2.2.2. Consolidation Phase

Subjects who achieve a CR or CRi at the end of the Induction Phase will enter the Consolidation Phase. The following are the options for consolidation therapy:

- Treatment with quizartinib/placebo plus cytarabine (4 cycles, if tolerated); or
- Allogeneic HSCT; or

- Treatment with quizartinib/placebo plus cytarabine followed by allogeneic HSCT.

Cytarabine will be administered by IV infusion every 12 hours on Days 1, 3, and 5 for a total of 6 doses. Quizartinib/placebo will be administered orally once a day from Day 6 to Day 19 (14 days). If quizartinib/placebo is interrupted, missed doses will not be made up.

Each cycle in the Consolidation Phase will be 28 days in duration. The subjects will receive 4 cycles of consolidation therapy, if tolerated. At the investigator's discretion, to allow for blood counts to recover, the subsequent Consolidation cycle may start up to 60 days after Day 1 of the previous cycle.

A bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected for local and central pathology in the first and last cycles of Consolidation, upon count recovery from Day 21 to Day 56.

See Section 4.1.2 for eligibility criteria to proceed into the Consolidation Phase, Section 5.4.2 for specific treatment administration requirements during the Consolidation Phase, and Section 6.2.2 and Table 17.4 for all procedures to be done during the Consolidation Phase.

3.2.2.2.1. Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT is one of the options for consolidation therapy, either alone or following consolidation treatment with cytarabine and quizartinib/placebo. Allogeneic HSCT that is performed for other reasons, eg, molecular relapse, will be considered nonprotocol-specified AML therapy, and the subject will be discontinued from quizartinib/placebo but will continue to be followed for outcome data.

In general, subjects are permitted to undergo **allogeneic** HSCT between the end of the Induction Phase and the start of the Continuation Phase. Under certain circumstances, a subject may undergo allogeneic HSCT for consolidation within the first 3 months of the Continuation Phase (see Section 6.2.2.2).

The investigator will be responsible to contact the transplant center on a regular basis to collect required data. Once the subject is able, the subject will return to the clinic for site visits every 4 weeks. See Section 6.2.2.2 and Table 17.5 for details.

For subjects who undergo allogeneic HSCT, treatment with quizartinib/placebo should be discontinued 7 days before the start of a conditioning regimen. Subjects may begin continuation therapy anytime between 30 to 180 days after the allogeneic HSCT. The site should follow their local procedures for allogeneic HSCT conditioning and recovery.

Subjects are **not** permitted to undergo autologous HSCT at any time during the study. Subjects who undergo autologous HSCT will be discontinued from quizartinib/placebo but will continue to be followed for outcome data.

3.2.2.3. Continuation Phase (up to 36 cycles)

Following consolidation therapy, subjects will enter the Continuation Phase if they meet the inclusion criteria (see Section 4.1.3). In addition, per investigator discretion, subjects who have achieved CR or CRi following Induction, but who are unable to receive consolidation therapy, will be permitted to enter the Continuation Phase if they meet the inclusion criteria.

During the Continuation Phase subjects will be treated with quizartinib/placebo once daily for up to 36 cycles. Continuation therapy will begin after induction or consolidation therapy, including allogeneic HSCT, and will continue until relapse, start of nonprotocol specified AML treatment, death, unacceptable toxicity, study close, or completion of 36 cycles, whichever occurs first.

The cycles during the Continuation Phase will be 28 days each, with no breaks in dosing between cycles. If quizartinib/placebo is interrupted, missed doses will not be made up.

Subjects will have their blood counts monitored at least every 4 weeks and will have a bone marrow exam every 12 weeks for 48 weeks and then every 24 weeks until week 96.

See Section 4.1.3 for eligibility criteria to proceed into the Continuation Phase, Section 5.4.3 for specific treatment administration requirements during the Continuation Phase, and Section 6.2.3 and Table 17.6 for all procedures to be done during the Continuation Phase.

3.2.2.4. Long Term Follow-up Phase

Subjects who complete 36 cycles of quizartinib/placebo in the Continuation Phase or permanently discontinue quizartinib/placebo in the Induction, Consolidation, or Continuation Phases will enter the Long-term Follow-up Phase, as detailed in Section 6.4.2.

4. STUDY POPULATION

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria – Randomization

Subjects must satisfy all of the following criteria to be randomized:

1. Must be competent and able to comprehend, sign, and date an Ethics Committee (EC)- or Institutional Review Board (IRB)- approved Informed Consent Form (ICF) before performance of any study-specific procedures or tests;
2. ≥18 years or the minimum legal adult age (whichever is greater) and ≤75 years (at Screening);
3. Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, based on the World Health Organization (WHO) 2008 classification (at Screening);[36]
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix 17.6 for descriptions) (at the time the subject signs their first informed consent form);
5. Presence of FLT3-ITD activating mutation in bone marrow (allelic ratio of ≥3% FLT3-ITD/total FLT3) (Section 6.1.2);
6. Subject is receiving standard “7+3" induction chemotherapy regimen as specified in the protocol (see Section 5.4.1 for required anthracycline and cytarabine doses);
7. Adequate renal function defined as:
   a. Creatinine clearance >50 mL/min, as calculated with the modified Cockcroft Gault equation (Appendix 17.9);
8. Adequate hepatic function defined as:
   a. Total serum bilirubin (TBL) ≤1.5 × upper limit of normal (ULN) unless the subject has documented Gilbert’s syndrome or the increase is related to increased unconjugated (indirect) bilirubin due to hemolysis;
   b. Serum alkaline phosphatase, aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 × ULN;
9. Serum electrolytes within the institution’s normal limits: potassium, calcium (total calcium, calcium corrected for serum albumin in case of hypoalbuminemia [Section 17.11.1], or ionized calcium) and magnesium. If outside of the institution’s normal range, subject will be eligible when electrolytes are corrected;
10. If a woman of childbearing potential, must have a negative serum pregnancy test upon entry into this study and must be willing to use highly effective birth control (Appendix 17.2) upon enrollment, during the treatment period and for 6 months following the last dose of investigational drug or cytarabine, whichever is later. A woman is considered of childbearing potential following menarche and until becoming

postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy);

11. If male, must be surgically sterile or willing to use highly effective birth control (Appendix 17.2) upon enrollment, during the treatment period, and for 6 months following the last dose of investigational drug or cytarabine, whichever is later.

4.1.2. Inclusion Criteria – Consolidation Phase

Subjects must satisfy all of the following criteria to start the Consolidation Phase and receive consolidation therapy:

1. Achieved CR or CRi (as defined in Table 17.15), based on local laboratory results, at the end of the Induction Phase;
2. Able to begin Consolidation Phase within 60 days of Day 1 of the last Induction Cycle.

4.1.3. Inclusion Criteria – Continuation Phase

Subjects must satisfy all of the following criteria to start the Continuation Phase and receive continuation therapy:

1. Subject does not have active acute, or ≥ Grade 3 GVHD
2. Subject has not initiated therapy for active GVHD (prophylaxis is allowed) within 21 days;
3. Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results, performed within 28 days prior to Cycle 1 Day 1 of continuation therapy;
4. Absolute neutrophil count (ANC) >500/mm^3 and platelet count >50,000/mm^3 without platelet transfusion support within 24 hours prior to Cycle 1 Day 1 of continuation therapy;
5. Able to begin Continuation Phase within 60 days of Day 1 of the last Consolidation cycle received or within 180 days after allogeneic HSCT (ie, stable after transplant).

4.2. Exclusion Criteria

Subjects who meet any of the following criteria are not eligible to be randomized:

1. Diagnosis of acute promyelocytic leukemia (APL), French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or BCR-ABL positive leukemia (ie, chronic myelogenous leukemia in blast crisis); subjects who undergo diagnostic workup for APL and treatment with ATRA, but who are found not to have APL, are eligible (treatment with ATRA must be discontinued before starting induction chemotherapy).
2. Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms;
3. Prior treatment for AML, except for the following allowances:
   a. Leukapheresis;

   b. Treatment for hyperleukocytosis with hydroxyurea;
   c. Cranial radiotherapy for central nervous system (CNS) leukostasis;
   d. Prophylactic intrathecal chemotherapy;
   e. Growth factor/cytokine support;

4. Prior treatment with quizartinib or other FLT3-ITD inhibitors;
5. Prior treatment with any investigational drug or device within 30 days prior to Randomization (within 2 weeks for investigational or approved immunotherapy) or currently participating in other investigational procedures;
6. History of known CNS leukemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture is recommended for subjects with symptoms of CNS leukemia to rule out extramedullary CNS involvement;
7. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated with no evidence of disease for at least 2 years;
8. Uncontrolled or significant cardiovascular disease, including any of the following:
   a. Bradycardia of less than 50 beats per minute, unless the subject has a pacemaker;
   b. QTcF interval >450 ms;
   c. Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome);
   d. Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;
   e. History of clinically relevant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes);
   f. History of second (Mobitz II) or third degree heart block (subjects with pacemakers are eligible if they have no history of fainting or clinically relevant arrhythmias while using the pacemaker);
   g. History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to Screening;
   h. History of New York Heart Association Class 3 or 4 heart failure;
   i. Left ventricular ejection fraction (LVEF) ≤45% or less than the institutional lower limit of normal per multi-gated acquisition scan (MUGA) or echocardiogram done within 30 days prior to randomization;
   j. Complete left bundle branch block;
9. Active acute or chronic systemic fungal, bacterial, or viral infection not well controlled by antifungal, antibacterial or antiviral therapy;
10. Known active clinically relevant liver disease (eg, active hepatitis B, or active hepatitis C)
11. Known history of human immunodeficiency virus (HIV). Subjects should be tested for HIV prior to Randomization if required by local regulations or EC;
12. History of hypersensitivity to any excipients in the quizartinib/placebo tablets;
13. Females who are pregnant or breastfeeding;
14. Otherwise considered inappropriate for the study by the investigator.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)

Subjects will be randomized to either the quizartinib group or the placebo group.

5.1.2. Method of Treatment Allocation

Subjects will be randomized into 1 of the 2 treatment groups (quizartinib or placebo) in a 1:1 ratio. The randomization will be stratified by age, region, and WBC count at the time of diagnosis of AML. Randomization will be managed through an Interactive Web/Voice Response System (IXRS).

5.1.3. Blinding

This study has a double-blind design. Quizartinib is supplied as 20 mg and 30 mg tablets. Placebo is supplied as tablets that match the appearance of the quizartinib 20 mg and 30 mg tablets. Neither the subjects nor any of the investigators, sponsor, or contract research organizations (CROs) will be aware of the treatments received.

An independent biostatistician, not otherwise part of the sponsor study team, will generate the randomization schedule.

5.1.4. Emergency Unblinding Procedure

In the case of an emergency where, in the opinion of the investigator, the study treatment assignment must be unblinded in order to evaluate further a course of medical treatment, it is required that the investigator discuss the case with the Medical Monitor, but the discussion may occur after unblinding if the subject requires emergency treatment. (Contact information – refer to the study reference materials).

In the event of unblinding, information about the treatment assignment **must be** restricted to designated Study Center staff/personnel that are providing immediate care to the subject. Any documentation of the treatment assignment **must be** maintained separately (ie, a secured file). The information **must not be** included in the subject's primary source files to ensure the treatment assignment will remain blinded to the Sponsor and study personnel not involved with the subject's immediate care.

5.2. Study Drugs

5.2.1. Quizartinib

Quizartinib is supplied to the Study Center as 20 mg tablets or 30 mg tablets. Each 20 mg tablet contains 20 mg quizartinib dihydrochloride (17.7 mg free base), and each 30 mg tablet contains 30 mg quizartinib dihydrochloride (26.5 mg free base).

All packages are shipped at conditions depicted on the product label. A temperature monitoring device will accompany every shipment to the Study Center from the Depot with instructions included within the shipment on how to process.

5.2.2. Placebo

Placebo is supplied to the Study Center as tablets matching the appearance of quizartinib 20 mg tablets and 30 mg tablets. All packages are shipped at conditions depicted on the product label. A temperature monitoring device will accompany every shipment to the Study Center from the Depot with instructions included within the shipment on how to process.

5.2.3. Description

The quizartinib and matching placebo will be supplied as round film-coated 20 mg (white) and 30 mg (yellow) tablets.

5.2.4. Labeling and Packaging

Double-blind study drug (quizartinib or matching placebo) will be provided in labeled high density polyethylene (HDPE) bottles. Each bottle will have a child-resistant cap and contain 30 tablets. The bottle label will include all information required by national and local regulations.

5.2.5. Preparation

Double-blind study drug (quizartinib or matching placebo) will be provided to Study Centers as fully prepared HDPE bottles. Bottles will be individually numbered. Assignment of bottles to subjects will be done via the IXRS.

There is no additional preparation required for quizartinib or matching placebo. Additional instructions for the handling of quizartinib/placebo will be provided in the study pharmacy manual.

5.2.6. Storage

Double-blind study drug supplies (quizartinib or matching placebo) must be stored appropriately in a locked cabinet/room with limited and controlled access under the recommended storage conditions. The required storage conditions are provided in the pharmacy manual.

NOTE: If storage conditions go outside of the recommended storage conditions, the Study Center must not dispense the affected supplies (affected supplies should be placed in quarantine per IXRS requirements). Proper notification processes must be followed immediately after receipt of quizartinib/placebo identified as having a temperature excursion.

5.2.7. Drug Accountability

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

In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment. This process is also documented on the Shipment Temperature Record and Excursion Reporting Form that is included with each shipment.

A Drug Accountability Record must be kept current and must contain the dates and quantities of study drug (quizartinib/placebo) received and any other medications supplied by the sponsor, the

subject's identification number and/or initials or supply number (as applicable), the date and quantity of quizartinib/placebo dispensed and remaining (in tablets), as well as the initials of the dispenser.

At the end of the study, or as directed, all quizartinib/placebo supplies, including unused, partially used, or empty containers, will either be destroyed at the site or be returned to a designee as instructed by Sponsor. Quizartinib/placebo will be returned or destroyed locally only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of quizartinib/placebo must be documented and the documentation included in the shipment. At the end of the study, a final reconciliation statement of quizartinib/placebo must be completed by the investigator or designee and provided to the Sponsor. Unused supplies of quizartinib/placebo may be destroyed by the investigator when approved in writing by Sponsor and Sponsor has received copies of the study center's drug handling and disposition standard operating procedures and it is assured that the sponsor will receive copies of the certificate of destruction which is traceable to the quizartinib/placebo tablets. Destruction of study drug at the Study Center is preferred.

5.3. Standard Chemotherapy

Subjects will receive commercially available cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin).

Refer to the cytarabine and anthracycline package insert or appropriate local (ie, country specific) labeling for detailed description of administration and potential risks associated with cytarabine and anthracycline.

Dose adjustments for renal and hepatic function are permitted per local package insert, labeling, or institutional guidelines.

5.4. Administration

This section describes the administration of double-blind study drug (quizartinib or matching placebo) as well as induction and consolidation chemotherapy.

Quizartinib/placebo can be taken either with or without food. Subjects should be encouraged to take quizartinib/placebo at the same time every day (for example, the morning) to encourage compliance. If the subject omits to take quizartinib in the morning, it may be taken later in the day (until midnight); otherwise the dose is considered missed. If the subject vomits after taking quizartinib/placebo, no replacement dose should be given. If quizartinib/placebo is interrupted, missed doses will not be made up. Do not double the dose of quizartinib/placebo the next day if a dose was missed.

If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed in each cycle. If delayed, best efforts should be made to begin administration of quizartinib/placebo as soon as possible.

5.4.1. Induction Phase (up to 2 cycles)

Subjects are permitted to receive up to 2 cycles of induction chemotherapy. Subjects with ≥5% blasts, per the Cycle 1 Days 21 to 28 bone marrow (or a later bone marrow if the Days 21 to

28 bone marrow does not allow for an accurate assessment of response), may receive a second cycle of induction chemotherapy, if appropriate.

Cycle 1

Cycle 1, Day 1 is defined as the start date of the chemotherapy infusions.

Cytarabine (cytosine arabinoside) 100 mg/m^2/day (200 mg/m^2/day allowed if this is the institutional or local standard) will be administered by continuous IV infusion for a total of 7 days, starting on Day 1 and ending on Day 8.

One of the following anthracycline regimens (investigator's choice) will be administered:

- Daunorubicin 60 mg/m^2/day IV infusion on Days 1, 2, and 3; or
- Idarubicin 12 mg/m^2/day IV infusion on Days 1, 2, and 3.

Subjects will be randomized on Day 7. If necessary, Randomization may be performed later (eg, Days 8 to 10) to allow time for addressing electrolyte abnormalities, QTcF prolongation, etc.

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing should start following the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to start within 3 days of Randomization if possible. If quizartinib/placebo cannot be started within 3 days of Randomization, please contact the Medical Monitor. The dose will be 40 mg/day (2 × 20 mg tablets). For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose will be reduced from 40 mg/day to 20 mg/day (Section 5.6.4). If quizartinib/placebo is interrupted, missed doses will not be made up.

Cycle 2

At the investigator's discretion, to allow for blood counts to recover or other reasons, the second Induction cycle may start up to 60 days after Day 1 of the first Induction cycle. It is recommended to wait at least 7 days after the last dose of quizartinib/placebo in Cycle 1 of Induction before starting Cycle 2 of Induction, since quizartinib has a long elimination half-life and there are no data on the safety of administering anthracycline within 7 days following quizartinib administration.

For Cycle 2 of Induction, investigators may choose to administer 1 of the following:

- "7+3" chemotherapy regimen, defined as 7 days of continuous IV infusion of standard dose cytarabine plus 3 days of anthracycline (the same anthracycline must be used throughout the Induction phase); OR
- "5+2" chemotherapy regimen, defined as 5 days of continuous IV infusion of standard dose cytarabine plus 2 days of anthracycline (the same anthracycline must be used throughout the Induction Phase).

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will start following the end of the cytarabine infusion, normally on Cycle 2, Day 8 or Cycle 2, Day 6, depending on the chemotherapy regimen selected by the investigator (ie, "7+3" or "5+2", respectively). If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. The dose will be

40 mg/day. For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose will be reduced from 40 mg/day to 20 mg/day. If quizartinib/placebo is interrupted, missed doses will not be made up.

5.4.2. Consolidation Phase

Cytarabine will be given on Days 1, 3, and 5. The cytarabine regimen will be:

- for subjects <60 years old: cytarabine 3.0 g/m^2 by IV infusion, every 12 hours for a total of 6 doses; or
- for subjects ≥60 years old: cytarabine 1.5 g/m^2 by IV infusion, every 12 hours for a total of 6 doses.

Subjects who are unable to tolerate a full cycle of consolidation chemotherapy are not required to complete the full cycle of chemotherapy in any cycle during the Consolidation Phase (4 Cycles, if tolerated).

Quizartinib/placebo will be administered orally once daily for 14 days starting on Day 6. If quizartinib/placebo dosing cannot begin as scheduled, the start of dosing may be delayed but best efforts should be made to begin as soon as possible. The dose will be 40 mg/day (2 × 20 mg tablets). The dose will be reduced from 40 mg/day to 20 mg/day (1 × 20 mg tablet) when subjects are concomitantly receiving strong CYP3A4 inhibitors (Section 5.6.4). If quizartinib/placebo is interrupted, missed doses will not be made up.

5.4.3. Continuation Phase (up to 36 cycles)

Quizartinib/placebo continuation therapy will begin after induction or consolidation therapy (including allogeneic HSCT) upon blood count recovery ANC >500/mm^3 and platelet count >50,000/mm^3 without a platelet transfusion within 24 hours of drawing blood samples). Quizartinib/placebo will be administered orally once daily starting on Day 1, with no breaks in dosing between cycles. If quizartinib is interrupted, missed doses will not be made up. Quizartinib/placebo continuation therapy will continue for up to 36 cycles after induction or consolidation, (as defined in Section 3.2.2.3) until: relapse, start of nonprotocol specified AML treatment, death, unacceptable toxicity, study close, or completion of 36 cycles, whichever occurs first.

The dose of quizartinib/placebo on Cycle 1, Days 1 to 15 will be 30 mg (1 × 30 mg tablet) orally once daily. On Cycle 1, Day 16, the dose will be increased to 60 mg/day (2 × 30 mg tablets) if the average QTcF of the triplicate ECGs is ≤450 ms on Cycle 1, Day 15. Once the dose is increased to 60 mg/day, the subject may continue on this dose as long as dose reduction is not needed.

For subjects concomitantly receiving a strong CYP3A4 inhibitor, the dose of quizartinib/placebo on Cycle 1, Days 1 to 15 will be 20mg (1 × 20mg tablet) orally once daily. On Cycle 1, Day 16, the dose will be increased to 30mg/day (1 × 30mg tablets) if the average QTcF of the triplicate ECG is ≤450 ms on Cycle 1, Day 15.

If the dose of quizartinib/placebo is not able to be increased on Cycle 1, Day 16, the dose may be increased on Cycle 2, Day 2 if the average QTcF of the triplicate ECG is ≤450 ms on Cycle 2, Day 1.

Subjects who permanently discontinued quizartinib/placebo because they completed 12 cycles of continuation therapy (as required in protocol Versions 1.0 and 2.0) may be restarted at the discretion of the investigator after discussion with the Medical Monitor. Subjects who restart therapy will receive double-blind continuation therapy in the same treatment group (quizartinib or placebo) to which they were randomized.

5.5. Control Treatment

The control treatment will be placebo tablets matching the appearance of quizartinib 20 mg and 30 mg tablets.

5.6. Quizartinib/Placebo Dose Reductions and Dosing Interruptions

The following are reasons for quizartinib/placebo dose reduction or dosing interruption:

- Adverse event: QTcF prolongation, other non-hematologic toxicities, or myelosuppression;
- Concomitant administration of a strong CYP3A4 inhibitor

See Table 5.1 for guidance on dose reductions and interruptions of quizartinib/placebo during the Induction, Consolidation, and Continuation Phases.

The dose of quizartinib/placebo will not be reduced lower than 30 mg/day in any phase of the study (not lower than 20 mg/day for subjects receiving strong CYP3A4 inhibitors).

If quizartinib/placebo is interrupted, doses will not be made up.

Table 5.1: Guidelines for Quizartinib/Placebo Dose Reductions and Dosing Interruptions

Induction Phase			
Full Dose	**AE, no concomitant strong CYP3A4 inhibitor**	**Concomitant strong CYP3A4 inhibitor[a]**	**AE and concomitant strong CYP3A4 inhibitor[a]**
40 mg/day	30 mg/day	20 mg/day	Interrupt[b]

AE=adverse event; CYP = cytochrome P450
[a] See Section 5.6.4 regarding increasing dose of study drug immediately after stopping strong CYP3A4 inhibitors.
[b] See Section pertaining to AE (Section 5.6.1, Section 5.6.2, or Section 5.6.3) for duration of interruption, missed doses will not be made up.

Consolidation Phase			
Full Dose	**AE, no concomitant strong CYP3A4 inhibitor**	**Concomitant strong CYP3A4 inhibitor[a]**	**AE and concomitant strong CYP3A4 inhibitor[a]**
40 mg/day	30 mg/day	20 mg/day	Interrupt[b]

AE=adverse event; CYP = cytochrome P450
[a] See Section 5.6.4 regarding increasing dose of study drug immediately after stopping strong CYP3A4 inhibitors.
[b] See Section pertaining to AE (Section 5.6.1, Section 5.6.2, or Section 5.6.3) for duration of interruption, missed doses will not be made up.

Continuation Phase				
	Full Dose	**AE, no concomitant strong CYP3A4 inhibitor**	**Concomitant strong CYP3A4 inhibitor[a]**	**AE and concomitant strong CYP3A4 inhibitor[a]**
Days 1-15	30 mg/day	Interrupt	20 mg/day	Interrupt[b]
Day 16 onward	60 mg/day	40 mg/day[c]	30 mg/day[d]	20 mg/day[e]

AE=adverse event; CYP = cytochrome P450
[a] See Section 5.6.4 regarding increasing dose of study drug immediately after stopping strong CYP3A4 inhibitors.
[b] See Section pertaining to AE (Section 5.6.1, Section 5.6.2, or Section 5.6.3) for duration of interruption, missed doses will not be made up.
[c] Can be further reduced to 30 mg/day, if necessary
[d] Can be further reduced to 20 mg/day, if necessary
[e] Can be interrupted if necessary.

5.6.1. QTcF Prolongation - Dose Interruptions and Reductions

Subjects taking quizartinib/placebo who experience QTcF prolongation >480 ms should be managed according to the guidelines below. For all episodes of QTc prolongation, regardless of grade, check electrolyte (potassium, calcium, and magnesium) levels and correct any abnormalities. If possible, stop any medications that may prolong the QT interval.

QTcF >480 ms ≤500 ms

- The dose of quizartinib/placebo will be reduced one level without interruption of dosing.

- Following dose reduction, the quizartinib/placebo dose may be resumed at the previous level in the next cycle if the QTcF has decreased to within 30 ms of baseline or <450 ms but subject must be monitored closely for QT prolongation for the first cycle at the increased dose.

QTcF >500 ms

- Quizartinib/placebo dosing will be interrupted for up to 14 days. If QTcF returns to within 30 ms of baseline or <450 ms within 14 days, quizartinib/placebo administration may be resumed at a reduced dose (reduce by one level).
- If QTcF >500 ms occurs during the Induction or Consolidation Phases, and if no cause other than quizartinib/placebo can be identified, then during the Continuation Phase, the dose of quizartinib/placebo cannot be escalated to 60 mg/day.

Recurrent QTcF>500 ms

- Permanently discontinue quizartinib/placebo if QTcF >500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (eg, serum electrolyte abnormalities, concomitant QT prolonging medication)

QTcF >500 ms or >60 ms change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

- Quizartinib/placebo dosing will be permanently discontinued.

5.6.1.1. Managing QTc Prolongation

Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the institution's normal range. If an electrolyte abnormality is identified, subjects should be monitored more frequently until levels normalize. Appropriate management should include ECG monitoring, reduction of serum electrolyte losses, replacement of electrolyte stores, and evaluation and treatment of associated toxicities.

Subjects should be monitored for the presence of hypokalemia at least 3 times per week during the Induction and Consolidation Phases of the study (see Section 6.2.1, Section 6.2.2.1, Section 17.1.1, and Section 17.1.2 for further details). If hypokalemia occurs, oral or IV potassium supplementation should be administered, as clinically indicated, and serial potassium level monitoring should be performed until potassium levels normalize. In addition, the underlying cause of hypokalemia should be investigated to prevent further episodes, if possible. If Grade 3 hypokalemia occurs (potassium <3 mmol/L), IV potassium replacement, close subject follow-up, continuous ECG monitoring, and serial potassium level monitoring every 2 to 4 hours until recovery to Grade 1 should be considered.

Subjects should also be monitored for the presence of concomitant hypomagnesemia and hypocalcemia (using the institution's normal ranges) and, if present, then replacement therapy should be initiated. In addition, the underlying cause of these electrolyte abnormalities should be investigated to prevent further episodes, if possible.

Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects (Table 17.8).

Subjects who experience >480 ms QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved.

5.6.2. Non-Hematologic Toxicity

The following guidelines should be followed for subjects who develop Grade 3 or 4 non-hematologic toxicity that is at least possibly related to quizartinib/placebo and persisting >48 hours without improvement to ≤ Grade 2 or without waiting 48 hours if in the investigator's judgment the AE poses a serious risk to the subject:

- Dosing will be interrupted for up to 28 days.
  - If toxicity improves to ≤ Grade 1 within 28 days, treatment may be resumed at the previous dose.
  - If toxicity improves to ≤ Grade 2 within 28 days, treatment may be resumed at a reduced dose (1 level).
  - If toxicity does not improve/resolve within 28 days, then quizartinib/placebo will be discontinued.

5.6.2.1. Hepatic Events and Liver Enzyme Elevation

Elevation of liver enzymes that meet the criteria below should be investigated and the cause identified when possible:

- ALT >8 × ULN; or
- AST or ALT >5 × ULN for more than two weeks; or
- ALT or AST >3 × ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis; or
- ALT or AST >3 × ULN with TBL >2 × ULN.

Once the cause of liver enzyme elevation is identified, remove or treat the contributing cause. If the above criteria are met and the elevation is considered to be related or possibly related to quizartinib/placebo, then quizartinib/placebo dosing should be interrupted.

Liver enzyme level testing will be repeated at least weekly, or more frequently, based on degree of hepatic laboratory abnormality. If the liver enzyme levels return to baseline levels, quizartinib/placebo may be resumed at the full dose. If toxicity does not improve/resolve within 28 days, then quizartinib/placebo will be discontinued.

Upon resumption of quizartinib/placebo, if liver enzyme elevations recur, treatment may be resumed at a reduced dose following return to baseline levels.

5.6.2.1.1. Liver Safety Monitoring and Evaluations

Any subject who temporarily interrupts or permanently discontinues quizartinib/placebo due to confirmed liver enzyme abnormalities and/or jaundice in the absence of a known cause, must have an evaluation to determine the cause of the event.

Evaluation may include the following depending on the clinical situation:

- Medical history and physical exam, including focus on medications and substances used: alcohol, acetaminophen, azole antifungals, change in medication dosages, new medications added, over the counter medication use and recreational drug use. Check for change in diet or use of dietary supplements;
- Abdominal ultrasound;
- Hepatitis A, B, C, and E screening (anti-hepatitis A virus immunoglobulin M, hepatitis B surface antigen, anti-hepatitis C virus plus viral titer, and evaluation for Hepatitis E), antinuclear antibody and anti-Smith antibody, cytomegalovirus, Epstein Barr virus;
- Additional evaluations as deemed appropriate by the investigator to exclude other causes of liver enzyme and bilirubin elevations;
- All laboratory results, including local laboratory reference ranges are to be recorded.

5.6.2.2. Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis)

Sweet's syndrome can be idiopathic, malignancy associated, or drug induced.[37] The incidence of drug-induced Sweet's syndrome (DISS) following FLT3 inhibitor monotherapy is approximately 10% during the treatment period in the setting of relapsed/refractory AML.[38] DISS is unlikely to occur in the setting of concurrent cytoreduction with traditional chemotherapy due to suppression of terminal differentiation of FLT3-ITD myeloblasts and associated clinical manifestations.

Diagnostic criteria for DISS include abrupt onset of painful erythematous plaques or nodules, pyrexia >38°C, temporal relationship between drug ingestion and clinical presentation, temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids, and histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. Cardiac, pulmonary, and upper airway neutrophil infiltration can present as life-threatening emergencies.[37]

The symptoms of neutrophilic dermatosis can generally be managed with systemic corticosteroid administration. Other first-line systemic treatments for Sweet's syndrome include potassium iodide and colchicine.[37] The interruption or discontinuation of quizartinib is usually not required[38, 39] and discussion with the Medical Monitor is optional. However, for advanced Grade 3 or 4 toxicities the decision to continue, interrupt or discontinue quizartinib therapy must be made by the investigator based on the individual subject's condition, taking into account the risks and benefits of continuing quizartinib/placebo therapy, and in consultation with the Medical Monitor.

5.6.2.3. Pyoderma Gangrenosum

Pyoderma gangrenosum is characterized by multiple cutaneous ulcers with mucopurulent or hemorrhagic exudate.[40] This sterile neutrophilic dermatosis is known to occur in association with malignancy, infection, autoimmune disorders and drugs, eg, tyrosine kinase inhibitors.[41] There is no diagnostic test, since it is a diagnosis of exclusion. Extracutaneous manifestations of this neutrophilic dermatosis are reported somewhat less commonly than with Sweet's syndrome.

As with Sweet's Syndrome, the symptoms of neutrophilic dermatosis can generally be managed with systemic and/or topical corticosteroid administration, and discussion with the Medical Monitor is optional.[40] More severe cases may require immunosuppressive or immunomodulatory agents. For advanced Grade 3 or 4 toxicities, the decision to continue, interrupt or discontinue quizartinib therapy must be made by the investigator based on the individual subject's condition, taking into account the risks and benefits of continuing quizartinib/placebo therapy, and in consultation with the Medical Monitor.

5.6.2.4. Differentiation Syndrome

Quizartinib can cause terminal differentiation of AML blast cells in patients with relapsed or refractory disease, which may be associated with the development of differentiation syndrome and may be life-threatening or fatal if not treated.

Symptoms of differentiation syndrome are dyspnea, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, acute renal failure, musculoskeletal pain, and hyperbilirubinemia. Less commonly, differentiation syndrome might present with pulmonary hemorrhage or acute febrile neutrophilic dermatosis. Please refer to the current Quizartinib IB for additional details on differentiation syndrome.[2]

It is important to promptly recognize the signs and symptoms of differentiation syndrome and implement appropriate treatment. Subjects with suspected differentiation syndrome should promptly start treatment with systemic glucocorticoids and hemodynamic monitoring until improvement.

Please refer to Section 5.6.2 for guidance on quizartinib dose interruption and/or reduction.

5.6.3. Myelosuppression (Continuation Phase)

In the Continuation Phase, the dose of quizartinib/placebo may be reduced at the investigator's discretion if:

- The subject enters the Continuation Phase with hematologic recovery (CR or CRi [ANC $\geq$1000/mm^3 and/or platelet count is $\geq$100,000/mm^3]) and the platelet count becomes <100,000/mm^3 and/or ANC is <1000/mm^3 or;
- The subject enters the Continuation Phase without hematologic recovery (ANC >500/mm^3 and <1000/mm^3 and/or platelet count >50,000/mm^3 and <100,000/mm^3 without transfusion support) and the subject has been on continuation therapy for $\geq$8 weeks.

The dose of quizartinib/placebo may be reduced stepwise from 60 mg/day to 40 mg/day to 30 mg/day. For subjects experiencing myelosuppression requiring dose reduction while taking a dose of 30 mg/day (20 mg/day in subjects receiving a strong CYP3A4 inhibitor), dosing will be interrupted.

5.6.4. Strong CYP3A4 Inhibitors – Dose Modifications

For subjects receiving a concomitant strong CYP3A4 inhibitor, the dose of quizartinib/placebo will be reduced as follows:

- Induction and Consolidation Phases: The dose of quizartinib/placebo will be reduced from 40 mg/day to 20 mg/day.
- Continuation Phase: The dose of quizartinib/placebo will be reduced from 30 mg/day to 20 mg (eg, Cycle 1, Days 1 to 15), or from 60 mg to 30 mg (Day 16 onward).

Once the strong CYP3A4 inhibitor is discontinued, the dose of quizartinib/placebo will be resumed at the full dose (Table 5.1) when the inhibitor is withdrawn. **No washout is required for the strong CYP3A4 inhibitor before increasing the dose of quizartinib/placebo back to the full dose.**

No dose reduction is required when subjects are coadministered a moderate or weak CYP3A4 inhibitor. See Table 17.9 for a list of strong CYP3A4 inhibitors.

5.7. Method of Assessing Treatment Compliance

The following measures will be employed to ensure treatment compliance.

- In the Induction Phase, all subjects in this study will commence therapy as hospital inpatients and oral quizartinib/placebo will be administered under nursing supervision.
- Subjects discharged from the hospital with quizartinib/placebo during the Consolidation and Continuation Phases shall return as noted in the Schedule of Events for each Phase, Table 17.4 and Table 17.6, respectively, and compliance will be assessed by the returned tablet count.

5.8. Prior and Concomitant Medications

5.8.1. Prior Medication

All medications received by subjects within 28 days prior to Randomization will be recorded as prior medications.

5.8.2. Concomitant Medication (Drugs and Therapies)

Concomitant medications and therapies include all prescription, over-the-counter, and herbal remedies.

Information on concomitant medications will be collected from Randomization through 30 days after the last dose of quizartinib/placebo (does not apply to the allogeneic HSCT period until the subject is able to return to the site, see Section 6.2.2.2). However, information on subsequent anti-leukemic treatments will be collected throughout the Long-Term Follow-up Phase. Data collected will include medication name, indication, dose, start date, and stop date.

If a subject experiences nausea and/or vomiting after the first dose of quizartinib/placebo, the subject should receive antiemetics as clinically indicated prior to and after administration of

quizartinib/placebo. If a subject vomits after quizartinib/placebo dosing, a replacement dose of quizartinib/placebo will not be administered.

Dexamethasone or an equivalent ophthalmic steroid preparation (0.1% ophthalmic solution, starting 12 hours before and for 24 - 48 hours after completion of cytarabine), or Isotears may be used to prevent conjunctival and corneal pain.

Menstruating females may receive Depo-Provera or another suppressant of menses during the entire course of this protocol. Suppression of menses should be continued until the platelet count is ≥50,000/mm^3 without transfusion support.

5.8.2.1. Supportive Care

During the Induction Phase, growth factors (granulocyte-colony stimulating factor [G-CSF]) may be considered for subjects who are septic and who have a life-threatening infection, according to the Institutional standard of care.

Growth factors (G-CSF) may be administered during the Consolidation Phase. Growth factors (G-CSF) and pegylated G-CSF must be stopped 7 and 14 days, respectively, prior to the bone marrow aspiration in the absence of an urgent medical need for continuing G-CSF administration.

Antibiotics (eg, quinolone), antifungals, and antivirals may be used as standard of care for the prevention or treatment of infections. See Section 5.6.4 for dose requirements if these medications are strong CYP3A4 inhibitors.

5.8.3. Prohibited Concomitant Medications

Subjects may not receive concomitant chemotherapy, immunotherapy, radiotherapy, transplant, or any ancillary therapy for AML that is not specified in the protocol, or that is considered to be investigational (ie, used for non-approved indications(s) and in the context of a research investigation) while on quizartinib/placebo. See Section 4.2 (exclusion criterion 3) for permitted prior therapy. Donor lymphocyte infusion (DLI) after allogeneic HSCT is permitted.

Medications associated with QT/QTc prolongations are prohibited and are detailed in Appendix 17.4. Exceptions are made for antibiotics, antivirals, and antifungals that are used as standard of care for the prevention or treatment of infections or if the investigator believes that beginning therapy with a potentially QTc-prolonging medication (such as anti-emetic) is vital to an individual subject's care while on study. In that case, additional ECG monitoring will be performed at the commencement of such a medication or from when there is an increase in its dosage. See Section 5.6.1 for guidelines on monitoring and managing QTc prolongation.

Strong CYP3A4 inhibitors should be avoided if possible but may be given with a corresponding dose reduction for quizartinib/placebo. There are no restrictions for moderate or weak CYP3A4 inhibitors (See Table 17.9).

Strong or moderate CYP3A4 **inducers** must not be used.

If quizartinib is co-administered with drugs that are substrates of P-gp, increased concentrations of the substrate drugs are possible and caution should be exercised.

5.8.4. Prior and Concomitant Nondrug Treatment and Procedures

All nondrug treatments and procedures received by subjects within 28 days prior to Randomization through 30 days after the last dose of quizartinib/placebo will be recorded (does not apply to the allogeneic HSCT period until the subject is able to return to the site, see Section 6.2.2.2).

5.8.5. Previous and Concomitant Transfusions

All transfusions received by subjects within 28 days prior to Randomization through 30 days after the last dose of quizartinib/placebo will be recorded (does not apply to the allogeneic HSCT period until the subject is able to return to the site, see Section 6.2.2.2).

5.8.6. Previous Radiotherapy

All radiotherapy received by subjects within 28 days prior to Randomization will be recorded.

5.8.7. Hematopoietic Stem Cell Transplantation Treatment

The conditioning regimen, donor type, and procedures used during the allogeneic HSCT period will be recorded.

Donor lymphocyte infusion after allogeneic HSCT is permitted.

5.9. Subject Withdrawal/Discontinuation

5.9.1. Reasons for Permanent Discontinuation of Study Drug

Quizartinib/placebo will be permanently discontinued for any of the following reasons:

- Adverse Event:
  - Intolerable AE related to quizartinib/placebo, including Grade 4 QTcF prolongation;
  - Any clinical AE or abnormal laboratory test result indicating, in the investigator's opinion, that continued quizartinib/placebo dosing is not in the subject's best interest;
- Death;
- Refractory disease, as defined in Section 7.2;
- Relapse, as defined in Section 7.2;
- Institution of nonprotocol specified AML therapy (prophylactic intrathecal therapy and DLI are permitted);
- Pregnancy (see Section 9.6);
- Withdrawal by subject (**from study drug**). NOTE: A subject's decision to discontinue study drug is not the same as complete withdrawal from the study. If a subject decides to stop study drug, the investigator should discuss with the subject

that he or she will remain in the study (ie, continue with study visits and assessments, including EFS/OS follow-up);

- Study Terminated by Sponsor.

Investigators should contact the Medical Monitor if they want to permanently discontinue quizartinib/placebo for reasons other than those listed above. Permanent discontinuations of quizartinib/placebo including the reason should be recorded.

In case of questions regarding continuation of quizartinib/placebo, the investigator should consult with the Medical Monitor.

5.9.1.1. Long-Term Follow-up of Subjects after Permanent Discontinuation of Study Drug

The Long-Term Follow-up Phase begins upon completion of 36 cycles of quizartinib/placebo in the Continuation Phase or permanent discontinuation of quizartinib/placebo in any phase. See Section 6.4 for details on long-term follow-up requirements.

5.9.2. Withdrawal from Study

The total duration of subject participation in the study will be until one of the following occurs:

- Subject death;
- Study closure or termination;
- Subject withdrawal of consent from study participation (see Section 5.9.2.1); or
- Subject lost to follow-up (see Section 5.9.2.2).

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

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

5.9.2.1. Withdrawal of Consent from Study Participation

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

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation:

- Attendance at study visits per protocol;
- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at end of study);
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider);

- Trial personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records).

If the subject refuses all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow up, the investigator will document this as a withdrawal of consent in the medical record and in the case report form.

For subjects who withdraw consent as define above, study personnel will use local, regional, and national public records (in accordance with local law) to monitor vital status.

5.9.2.2. Subjects Lost to Follow-up

The investigator will make every effort not to have any subjects Lost to Follow-up. If a subject is potentially Lost to Follow-up (eg, missed study visits, unable to be contacted by phone), the investigator will make every effort to contact the subject before the subject is declared Lost to Follow-up (see Study Operations Manual for details). Once the Study Center has exhausted and documented all actions, the investigator should contact the study monitor for additional guidance and alternative options.

Subjects will not be classified as Lost to Follow-up unless all actions have been exhausted and documented.

6. STUDY PROCEDURES

A tabular summary of the visit schedule for the study is provided in Appendix 17.1.

During the various phases of the study a bone marrow aspirate will be required. If the aspirate is not sufficient or not feasible to obtain, then a core biopsy specimen may be obtained. In addition, if an unscheduled bone marrow examination is performed during any phase of the study, an aspirate specimen must be shipped to both the local and central laboratories for assessment and a blood sample should be obtained for hematology.

The FLT3-ITD MRD assessment is for the purposes of this study and results will therefore not be available until after the end of the study.

Laboratory reports with all local laboratory results from samples collected in all phases for hematology, serum chemistry (including potassium monitoring as well as hypomagnesemia and hypocalcemia), and coagulation are to be sent to the central laboratory for data entry.

Throughout the treatment period, urine or serum pregnancy tests are to be done at monthly intervals for women of childbearing potential (as defined in Section 4.1.1).

6.1. Screening (Days -7 to 6)

6.1.1. Overview of Screening

Subjects with newly diagnosed, morphologically documented AML (Section 4.1.1) will be screened. The Screening period is the time from 7 days prior to the start of induction chemotherapy up to the day of Randomization. It is anticipated that subjects will recently have had some or all of the screening tests done as part of routine care outside the auspices of this study. Results of these tests done as part of routine care may be used to qualify the subject (see timing requirements in Section 6.1.2). The subject does not need to repeat recently completed procedures/tests for study qualification.

Written informed consent must be obtained before any study-specific procedure is performed, including sending a bone marrow aspirate specimen (done as routine care) to the central laboratory for assessment of FLT3-ITD activating mutation. A separate screening ICF may be used to obtain consent to send the sample to the central laboratory, if desired.

Full documentation for the qualifying test results is required, including those done as part of routine care outside the auspices of this study.

6.1.2. Screening Procedures

The following activities and/or assessments will be performed at/during Screening:

- Review the subject's demographics, medical and AML disease history, including cytogenetic risk classification[42], and results of tests done as part of routine care and compare against the eligibility criteria (see Section 4) for randomization;
- Have the subject sign the ICF (must be done before any study-specific procedures are performed);
- Obtain subject identification number;

- Send a bone marrow aspirate specimen (obtained prior to the start of chemotherapy in the first Induction cycle) to the central laboratory for assessment of morphology and FLT3-ITD activating mutation.
  - If an aspirate specimen is not available:
    - Obtain a peripheral blood sample (obtained prior to the start of chemotherapy in the first Induction cycle) for assessment of FLT3-ITD activating mutation and send to the central laboratory.
    - If core biopsy is available, send to the central laboratory for assessment of morphology. If not, send aspirate slides (if available) to the central laboratory for assessment of morphology
- Collect results of the following tests (results of most recent tests done as part of routine care within 7 days prior to the start of induction chemotherapy may be used to qualify the subject):
  - Physical examination (Section 9.10);
  - Vital signs (blood pressure, pulse rate, respiratory rate, and temperature), height, weight, and body surface area (BSA);
  - 12-lead ECG (does not need to be performed on the study-supplied ECG machine);
  - MUGA or echocardiogram performed within 30 days prior to Randomization (subjects must have LVEF >45%); if not done as part of routine care, a MUGA or echocardiogram must be done and LVEF must be >45%;
  - Laboratory tests (Table 17.19):
    - Hematology;
    - Chemistry;
    - Coagulation;
    - Urinalysis;
    - HIV (if required by local regulations)
  - For women of childbearing potential (as defined in Section 4.1.1) document the results of a negative serum pregnancy test (if not performed as a part of routine care within 14 days of Randomization, must be performed with the results available prior to Randomization);
  - Copies of de-identified local pathology report from the bone marrow aspirate for submission to IRC;
- Assess and record the subject's ECOG performance status;
- Record all serious AEs (SAEs) related to any study procedure experienced by the subject since the initial ICF (FLT3-ITD Screening if applicable or Main Study) was signed and up to the day of Randomization;
- Record any treatments (drug and nondrug) given for SAEs related to a study procedure.

6.2. Treatment Period

6.2.1. Induction Phase (up to 2 cycles)

A specimen from all protocol-specified bone marrow aspirates (or a core biopsy specimen if aspirate cannot be obtained) must be sent to both the local and central laboratories for assessment. In addition, if an unscheduled bone marrow examination is performed, an aspirate specimen must be sent to both the local and central laboratories for assessment, and results of the local hematology will be collected.

Monitoring for the presence of hypokalemia should be performed at least 3 times per week during the Induction Phase and treatment instituted to maintain potassium within normal limits. Subjects should also be monitored for the presence of concomitant hypomagnesemia and hypocalcemia (per institution's normal ranges) and corrected if clinically indicated. See Section 5.6.1.1 for further details. The results are to be submitted to the central laboratory.

Response will be assessed based on the local laboratory results using the response criteria in Table 17.15.

6.2.1.1. Cycle 1

For the purpose of the study procedures and the schedule of events, Day 1 is defined as the first day of the first cycle of administration of induction chemotherapy.

Refer to the schedule of events for list of assessments and procedures to be performed in Cycle 1 of Induction (Table 17.1).

Randomization

Subjects will be randomized on Day 7. If necessary, Randomization may be performed later (eg, Days 8 to 10) to allow time for addressing electrolyte abnormalities, QTcF prolongation, etc. The investigator will contact the IXRS to randomize the subject and to assign quizartinib/placebo.

Subjects must be diagnosed as FLT3-ITD (+) in order to be randomized. Subjects will be randomized based on the FLT3-ITD central laboratory result, unless the FLT3-ITD central laboratory result is not available by Day 8, in which case the subjects may be randomized based on the FLT3-ITD local laboratory result. However, in all cases a bone marrow aspirate specimen (or blood sample taken before start of chemotherapy treatment if bone marrow aspirate specimen not available) must be sent for central determination of FLT3-ITD status.

In the cases where subjects have been randomized and the FLT3-ITD local and central laboratory results are discordant, the subjects will continue with quizartinib/placebo dosing.

6.2.1.1.1. Cycle 1, Day 7 (Window of Days 7 to 10)

- Once FLT3-ITD (+) confirmed, explain all study procedures, risks, and benefits to the subject; review the Main Study ICF with the subject; this may be done sooner than Day 7; answer all of the subject's questions; have the subject sign and date the most current approved version of the ICF. Subjects must receive a copy of their ICF;

- Confirm that the subject continues to meet all of the inclusion criteria and none of the exclusion criteria (see Section 4);
- Perform triplicate 12-lead ECG (must be obtained at least 1 minute apart), after the subject has been fully supine for 10 minutes. Triplicate ECGs must be obtained at least 1 minute apart;
  - If QTcF >450 ms (average of triplicate):
    - Contact the central ECG laboratory and request an expedited reading;
    - Electrolytes (potassium, calcium, and magnesium) should be checked and any values outside the institution's normal range should be corrected;
    - Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects (Table 17.8);
    - Perform repeat 12-lead ECG in triplicate. The QTcF (average of triplicate) must be ≤450 ms for randomization. Contact the central ECG laboratory and request an expedited reading. However, the pre-randomization triplicate ECG does not need to be repeated if the QTcF from the local ECG reading is >450 ms but the central laboratory reading is ≤450 ms;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis;
- For women of childbearing potential (as defined in Section 4.1.1) perform a serum pregnancy test and document the results within 14 days of Randomization (if performed in screening, this does not need to be repeated); subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 6 months of discontinuing the quizartinib/placebo (refer to Section 9.6);
- If the subject provides consent, collect pharmacogenomics and proteomic samples (blood and buccal swab) before administering quizartinib/placebo;
- Record all prior medications, nondrug treatments, transfusions, and radiotherapy the subject received within 28 days prior to Randomization, and review and document all current concomitant medications and transfusions the subject has received at Randomization;
- Record all AEs the subject experienced from Day 1 until the day of Randomization:
  - Record any treatments (drug and nondrug) given for AEs;
- Access the IXRS to randomize the subject.

6.2.1.1.2. Cycle 1, Day 8 (Start of Quizartinib/Placebo Administration)

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will start following the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo dosing cannot begin as scheduled, the start of dosing may be delayed but best efforts should be made to begin dosing within 3 days of Randomization, if possible. If quizartinib/placebo cannot be started within 3 days of Randomization, please contact the Medical Monitor. If quizartinib/placebo is interrupted, missed doses will not be made up.

The following activities and/or assessments will be performed on the first day of dosing, prior to quizartinib/placebo administration, unless otherwise noted:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG at: -0.5 to 0 hours predose and 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart.
  - The predose QTcF (average of triplicate) must be ≤450 ms to proceed with administration of the first dose of quizartinib/placebo. Contact the central ECG laboratory and request an expedited reading. However, there is no need to repeat the triplicate ECG at -0.5 to 0 hours predose if the QTcF from the local reading is >450 ms but the central laboratory reading is ≤450 ms.
- Collect a blood sample for sparse PK sampling at -0.5 to 0 hours predose and 2 to 4 hours (postdose), see further details in Table 8.1. Collect PK sample within 10 minutes after performing the ECG;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Perform 12-lead ECG (triplicate) at: -0.5 to 0 hours predose, 1, 2, 4, and 6 hours postdose, (Table 17.14). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
  - Collect blood samples for PK sampling at -0.5 to 0 hours predose, 1, 2, 4, and 6 hours postdose, see further details in Table 8.4. Collect PK sample within 10 minutes after performing the last triplicate ECG;
  - Collect blood samples for the PIA assay -0.5 to 0 hours predose and 2 hours postdose (Table 8.5), immediately after each respective PK sample collection;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo; the dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.1.3. Cycle 1, Days 9 through 14

The following activities and/or assessments will be performed on Cycle 1, Days 9 through 14, unless otherwise noted:

- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Perform 12-lead ECG (triplicate) 24 hours after the ECG reading on Day 8, Hour 0 (Table 17.14). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
  - Collect a blood sample for PK sampling determination 24 hours after the PK sample is collected on Day 8, Hour 0. See further details in Table 8.4. Collect PK sample within 10 minutes after performing the last triplicate ECG;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.1.4. Cycle 1, Day 15 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 15:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling at 2 to 4 hours postdose, see further details in Table 8.1. Collect PK sample within 10 minutes after performing the ECG;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for PK sampling at 2 to 4 hours postdose, see further details in Table 8.4. Collect PK sample within 10 minutes after performing the last triplicate ECG;
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after the PK sample collection;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.1.5. Cycle 1, Days 16 through 20

The following activities and/or assessments will be performed on Cycle 1, Days 16 through 20:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.1.6. Cycle 1, Day 21 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 21, prior to quizartinib/placebo administration, unless otherwise noted:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform 12-lead ECG (triplicate) 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling on Day 21 at: 2 to 4 hours postdose, see further details in Table 8.1. Collect PK sample within 10 minutes after the last triplicate ECG;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Perform 12-lead ECG (triplicate) on Day 21 at predose (-0.5 to 0 hours), 1, 2, 4, and 6 hours postdose (Table 17.14). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
  - Collect blood samples for PK on Day 21 at: predose (-0.5 to 0 hours), 1, 2, 4, and 6 hours postdose, see further details in Table 8.4. Collect PK sample immediately after performing the last triplicate ECG;
  - Collect a blood sample for the PIA assay 2 hours postdose (Table 8.5), immediately after PK sample collection;
- Review and document all concomitant medications and transfusions the subject has received;

- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- On Day 21 (window of Day 21 to Day 28):
  - Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
    - Collect a copy of de-identified local pathology report for submission to IRC;
  - On the day the bone marrow aspirate specimen is collected:
    - Collect and send blood samples to the laboratory for the following tests (Table 17.19):
      Hematology:
      - If additional hematology tests are performed within 14 days after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 1), submit the laboratory reports to Q2 Laboratory);

      Chemistry;
      Coagulation;
    - Conduct a physical examination (Section 9.10);
    - Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
  - Assess the subject's response based upon the local laboratory results using the Response Criteria (Table 17.15); if an accurate assessment of response cannot be made, then a bone marrow aspirate should be repeated upon count recovery or Day 56 (±3 Days), whichever occurs first.

6.2.1.1.7. Cycle 1, Day 22 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 22 unless otherwise specified:

- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Perform 12-lead ECG (triplicate) at: Day 22 at 24 hours (after Hour 0 ECG reading on Day 21) (Table 17.14). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
  - Collect a blood sample for PK sampling on Day 22 at 24 hours (after Hour 0 PK sample collected on Day 21), see further details in Table 8.4. Collect PK sample within 10 minutes after performing the last triplicate ECG;

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.1.8. Cycle 1, Day 21 to Day 56 (±3 Days or Count Recovery)

The following should be performed for subjects for whom there is a plan to perform a repeat bone marrow aspirate upon count recovery or at Day 56 ±3 days:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.
- Collect and send blood samples to the laboratory, at least weekly until counts have recovered, for the following tests (Table 17.19):
  - Hematology
  - Chemistry

6.2.1.1.9. Cycle 1, Day 28 (±3 Days)

The following activities and/or assessments will be performed on Cycle 1, Day 28:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures on the last day of the Induction Phase;
- Assess and record the subject's ECOG performance status;
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.1.10. Cycle 1, Day of Repeat Bone Marrow Aspirate (if required; upon count recovery or up to Day 56 ± 3 Days)

The following activities and/or assessments will be performed if a repeat bone marrow is required to determine response, upon count recovery or up to Cycle 1, Day 56:

- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Record all healthcare resource utilization since the last visit (see Section 10.2)

- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology:
    - If additional hematology tests are performed within 14 days before or after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 1), submit the laboratory reports to Q2 Laboratory;
  - Coagulation;
- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject based upon the local laboratory results using the Response Criteria (Table 17.15);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.2. Cycle 2

Subjects with ≥5% blasts, per the final bone marrow in Cycle 1 (local laboratory results), may receive a second cycle of induction chemotherapy, if considered appropriate in the judgment of the investigator (reason for not administering a second cycle should be documented).

Assessments and procedures for Cycle 2 Day 1 do not need to be repeated if they were done for Cycle 1 within the prior 7 days. Refer to the schedule of events for the list of assessments and procedures to be performed in Cycle 2 of Induction (Table 17.2 and Table 17.3).

It is recommended to wait at least 7 days after the last dose of quizartinib/placebo in Cycle 1 of Induction before starting Cycle 2 of Induction, since quizartinib has a long elimination half-life and there are no data on the safety of administering anthracycline within 7 days following quizartinib administration.

6.2.1.2.1. Cycle 2, "7+3" Chemotherapy Regimen

This section describes the procedures to be followed if the subject receives a "7+3" regimen in Cycle 2. See Section 6.2.1.2.2 for the procedures to be followed if the subject receives a "5+2" regimen in Cycle 2.

6.2.1.2.1.1. Cycle 2, Day 1 ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2 Day 1 prior to cytarabine and anthracycline administration, unless otherwise noted (activities and/or assessments performed within 7 days prior to Day 1 do not need to be repeated):

- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight and BSA (calculated from the height recorded at Screening);
- Assess and record the subject's ECOG performance status;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs since Screening;
- Administer anthracycline as an IV infusion (refer to Section 5.4.1 for anthracycline drug administration);
- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.1.2. Cycle 2, Days 2 and 3 ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2 Days 2 and 3:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer anthracycline as an IV infusion (refer to Section 5.4.1 for anthracycline drug administration);

- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.1.3. Cycle 2, Days 4 to 7 ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 4 to 7:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.1.4. Cycle 2, Day 8 ("7+3" Chemotherapy Regimen)

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will begin after the end of the cytarabine infusion, normally on Day 8. If quizartinib/placebo dosing cannot begin as scheduled, the start of dosing may be delayed but best efforts should be made to begin dosing as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

The following activities and/or assessments will be performed on the day of the start of quizartinib/placebo administration (usually Cycle 2, Day 8) prior to quizartinib/placebo administration, unless otherwise noted:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG on Day 8 at predose (-0.5 to 0 hours) and 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;

- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.1.5. Cycle 2, Days 9 through 14 ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 9 through 14:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.1.6. Cycle 2, Day 15 (±1 Day) ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 15:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.1.7. Cycle 2, Days 16 through 20 ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 16 through 20:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;

- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.1.8. Cycle 2, Day 21 (±1 Day) ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 21, prior to quizartinib/placebo administration, unless otherwise noted:

- Perform 12-lead ECG (triplicate) 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- On Day 21 (window of Day 21 to Day 28):
  - Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
    - Collect a copy of de-identified local pathology report for submission to IRC;
  - On the day the bone marrow aspirate specimen is collected:
    - Collect and send blood samples to the laboratory for the following tests (Table 17.19):
      Hematology:
      - If additional hematology tests are performed within 14 days after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 2), submit the laboratory reports to Q2 Laboratory;

      Chemistry;
      Coagulation;
    - Conduct a physical examination (Section 9.10);
    - Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
  - Assess the subject's response based upon the local laboratory results using the Response Criteria (Table 17.15); if an accurate assessment of response cannot be made, then a bone marrow aspirate should be repeated upon count recovery or Day 56 (±3 Days), whichever occurs first.

6.2.1.2.1.9. Cycle 2, Day 21 to Day 56 ±3 Days or Count Recovery

The following should be performed for subjects for whom there is a plan to perform a repeat bone marrow aspirate upon count recovery or at Day 56 ±3 days:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.
- Collect and send blood samples to the laboratory, at least weekly until counts have recovered, for the following tests (Table 17.19):
  - Hematology
  - Chemistry

6.2.1.2.1.10. Cycle 2, Day 28 (±3 Days) ("7+3" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 28:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures on the last day of the Induction Phase;
- Assess and record the subject's ECOG performance status;
- Record all healthcare resource utilization since the last visit (see Section 10.2)
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.2.1.11. Cycle 2, "7 + 3" Chemotherapy Regimen, Day of Repeat Bone Marrow Aspirate (if required; upon count recovery or up to Day 56 ±3 days)

- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology:
    - If additional hematology tests are performed within 14 days before or after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 2), submit the laboratory reports to Q2 Laboratory;
  - Coagulation;

- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject based upon the local laboratory results using the Response Criteria (Table 17.15);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.2.2. Cycle 2, "5+2" Chemotherapy Regimen

6.2.1.2.2.1. Cycle 2, Day 1 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 1 prior to cytarabine and anthracycline administration, unless otherwise noted (activities and/or assessments performed within 7 days prior to Day 1 do not need to be repeated):

- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight and BSA (calculated from the height recorded at Screening);
- Assess and record the subject's ECOG performance status;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs since Screening;

- Administer anthracycline as an IV infusion (refer to Section 5.4.1 for anthracycline drug administration);
- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.2.2. Cycle 2, Day 2 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2 Day 2:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer anthracycline as an IV infusion (refer to Section 5.4.1 for anthracycline drug administration);
- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.2.3. Cycle 2, Days 3 to 5 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 3 to 5:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer cytarabine as a continuous IV infusion (refer to Section 5.4.1 for cytarabine drug administration).

6.2.1.2.2.4. Cycle 2, Day 6 ("5+2" Chemotherapy Regimen)

Quizartinib/placebo will be administered orally once daily for 14 days. Dosing will start following the end of the cytarabine infusion, normally on Day 6. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed but best efforts should be made to begin dosing as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

The following activities and/or assessments will be performed on the Day of the start of quizartinib/placebo administration (usually Cycle 2, Day 6), prior to quizartinib/placebo administration, unless otherwise noted:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG at: predose (-0.5 to 0 hours) and 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;

- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.2.5. Cycle 2, Days 7 through 12 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 7 through 12:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.2.6. Cycle 2, Day 13 (±1 Day) ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 13:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:

  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.2.7. Cycle 2, Days 14 through 18 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Days 14 through 18:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.2.8. Cycle 2, Day 19 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 19, prior to quizartinib/placebo administration, unless otherwise noted:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform 12-lead ECG (triplicate) 2 to 4 hours postdose (Table 17.11). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.1.2.2.9. Cycle 2, Day 21 ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 2, Day 21 (window of Day 21 to Day 28):

- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- On the day the bone marrow aspirate specimen is collected:

  - Collect and send blood samples to the laboratory for the following tests (Table 17.19):
    Hematology:
    - If additional hematology tests are performed within 14 days after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 2), submit the laboratory reports to Q2 Laboratory;

    Chemistry;
    Coagulation;
  - Conduct a physical examination (Section 9.10);
  - Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Assess the subject's response based upon the local laboratory results using the Response Criteria (Table 17.15); if an accurate assessment of response cannot be made, then a bone marrow aspirate should be repeated upon count recovery or Day 56 (±3 days), whichever occurs first.
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;

6.2.1.2.2.10. Cycle 2, Day 21 to Day 56 ±3 Days or Count Recovery

The following should be performed for subjects for whom there is a plan to perform a repeat bone marrow aspirate upon count recovery or at Day 56 ±3 days:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.
- Collect and send blood samples to the laboratory, at least weekly until counts have recovered, for the following tests (Table 17.19):
  - Hematology
  - Chemistry

6.2.1.2.2.11. Cycle 2, Day 28 (±3 Days) ("5+2" Chemotherapy Regimen)

The following activities and/or assessments will be performed on Cycle 1, Day 28:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures on the last day of the Induction Phase;
- Assess and record the subject's ECOG performance status;
- Record all healthcare resource utilization since the last visit (see Section 10.2);

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.1.2.2.12. Cycle 2, "5 + 2" Chemotherapy Regimen, Day of Repeat Bone Marrow Aspirate (if required; upon count recovery or up to Day 56 ±3 days)

- Conduct a physical examination (Section 9.10);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology:
    - If additional hematology tests are performed within 14 days before or after the bone marrow aspirate specimen is collected (and before the end of Induction Cycle 2), submit the laboratory reports to Q2 Laboratory;
  - Coagulation;
- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject's response based upon the local laboratory results using the Response Criteria (Table 17.15);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.2. Consolidation Phase

6.2.2.1. Consolidation Chemotherapy (4 Cycles, if Tolerated)

At the investigator's discretion, to allow for blood counts to recover, the Consolidation cycle may start up to 60 days after Day 1 of the previous cycle.

Refer to the schedule of events for the list of assessments and procedures to be performed during the Consolidation Phase (Table 17.4).

A specimen from all protocol-specified bone marrow aspirates (or a core biopsy specimen if aspirate cannot be obtained) must be sent to the central laboratory for assessment. In addition, if an unscheduled bone marrow examination is performed, an aspirate specimen must be sent to both the local and central laboratories for assessment and a blood sample should be obtained for hematology. A bone marrow aspirate is collected in Cycle 1 and in the final cycle (eg, in Cycle 3 if the subject receives 3 cycles of consolidation therapy).

During the Consolidation Phase, monitoring for the presence of hypokalemia should be performed at least 3 times per week on the days of cytarabine administration. Potassium levels will also be checked when routine chemistry samples tests are being performed. If hypokalemia is identified, potassium should be monitored at least 3 times a week until the levels normalize. Subjects should also be monitored for the presence of concomitant hypomagnesemia and hypocalcemia (per institution's normal ranges) and corrected if clinically indicated. See Section 5.6.1.1 for further details. The results are to be submitted to the central laboratory.

6.2.2.1.1. Cycle 1, Day 1

The following activities and/or assessments will be performed on Cycle 1, Day 1 prior to cytarabine administration, unless otherwise noted (activities and/or assessments performed ≤7 days prior to Day 1 do not need to be repeated):

- Confirm that the subject meets all of the inclusion criteria for the Consolidation Phase (see Section 4.1.2);
- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight and BSA (calculated from the height recorded at Screening);
- Assess and record the subject's ECOG performance status;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test and document the results; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;

- Administer cytarabine 3.0 g/m^2 (for subjects <60 years old) or 1.5 g/m^2 (for subjects ≥60 years old) IV every 12 hours.

6.2.2.1.2. Cycle 1, Day 3 and Day 5

The following activities and/or assessments will be performed on Cycle 1, Day 3 and Day 5:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.
- Administer cytarabine 3.0 g/m^2 (for subjects <60 years old) or 1.5 g/m^2 (for subjects ≥60 years old) IV every 12 hours.

6.2.2.1.3. Cycle 1, Day 6 (+2 days) (Start of Quizartinib/Placebo)

Quizartinib/placebo will be administered orally once daily for 14 days, starting on Day 6. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

The following activities and/or assessments will be performed on Cycle 1, Day 6, prior to quizartinib/placebo administration, unless otherwise noted:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG predose (-0.5 to 0 hours) and 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.2;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- Review and document all concomitant medications and transfusions the subject has received;

- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- If the subject is being discharged from the hospital, then dispense quizartinib/placebo. Additionally, counsel the subject on the quizartinib/placebo dosing regimen for Days 7 to 12, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 13.

6.2.2.1.4. Cycle 1, Day 13 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 13:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect blood samples for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.2.
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;
- Collect and send blood samples to the laboratory tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- If outpatient, then counsel the subject on the quizartinib/placebo dosing regimen from Days 14 through 18, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 19.

6.2.2.1.5. Cycle 1, Day 19 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 19:

- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.2.
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance, if they were dispensed quizartinib/placebo bottles upon discharge.

6.2.2.1.6. Cycle 1, Day 21 to Day 56 ±3 Days or Count Recovery

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

Starting on Day 21, the following assessments should be performed at least weekly until counts have recovered:

- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology
  - Chemistry

The following activities and/or assessments will be performed upon count recovery, or Day 56 (±3 Days), whichever occurs first:

- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology. If an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- On the day the bone marrow aspirate specimen is collected:
  - Collect and send blood samples to the laboratory for the following tests (Table 17.19):
    - Hematology;
    - Chemistry;
  - Conduct a physical examination (Section 9.10);
  - Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Assess the subject for relapse based on the local laboratory results (see criteria in Section 7.2);

6.2.2.1.7. Cycle 1, Day 28 (±7 Days)

The following activities and/or assessments will be performed on Cycle 1, Day 28:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

If Cycle 1 is the last Consolidation cycle, see Section 6.2.2.1.14 for details on additional assessments.

6.2.2.1.8. Cycle 2, Cycle 3, and Cycle 4; Day 1

The following activities and/or assessments will be performed on Day 1 prior to cytarabine administration, unless otherwise noted (activities and/or assessments performed ≤7 days prior to Day 1 do not need to be repeated):

- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight and BSA (calculated from the height recorded at Screening);

- Assess and record the subject's ECOG performance status;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test and document the results; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer cytarabine 3.0 g/m^2 (for subjects <60 years old) or 1.5 g/m^2 (for subjects ≥60 years old) IV every 12 hours.

6.2.2.1.9. Cycle 2, Cycle 3, and Cycle 4; Day 3 and Day 5

The following activities and/or assessments will be performed on Day 3 and Day 5:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.
- Administer cytarabine 3.0 g/m^2 (for subjects <60 years old) or 1.5 g/m^2 (for subjects ≥60 years old) IV every 12 hours.

6.2.2.1.10. Cycle 2, Cycle 3, and Cycle 4, Day 6 (+2 Days) (Start of Quizartinib/Placebo)

Quizartinib/placebo will be administered orally once daily for 14 days, starting on Day 6. If quizartinib/placebo administration cannot begin as scheduled, the start of dosing may be delayed, but best efforts should be made to begin as soon as possible. If quizartinib/placebo is interrupted, missed doses will not be made up.

The following activities and/or assessments will be performed on Day 6 prior to quizartinib/placebo administration, unless otherwise noted:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);

- Perform triplicate 12-lead ECG predose (-0.5 to 0 hours) and 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day;
- If the subject is being discharged from the hospital, then dispense quizartinib/placebo. Additionally, counsel the subject on the quizartinib/placebo dosing regimen for Days 7 to 12, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 13.

6.2.2.1.11. Cycle 2, Cycle 3, and Cycle 4; Day 13 (±1 Day)

The following activities and/or assessments will be performed on Day 13:

- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood samples to the laboratory tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day;

- If outpatient, then counsel the subject on the quizartinib/placebo dosing regimen from Days 14 through 18, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 19.

6.2.2.1.12. Cycle 2, Cycle 3, and Cycle 4; Day 19 (±1 Day)

The following activities and/or assessments will be performed on Day 19:

- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.12). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance if they were dispensed quizartinib/placebo bottles upon discharge.

6.2.2.1.13. Cycle 2, Cycle 3, and Cycle 4; Day 28 (±7 Days)

The following activities and/or assessments will be performed on Day 28:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures (if this is the last day of the Consolidation Phase);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs.

6.2.2.1.14. Last Consolidation Cycle, Day 21 to Day 56 ±3 Days or Count Recovery

The following procedures will be done from Day 21 to Day 56 ±3 days or count recovery during the last Consolidation cycle before allogeneic HSCT or the start of the Continuation Phase:

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Starting on Day 21, collect weekly until counts have recovered, and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;

The following activities and/or assessments will be performed upon count recovery, or on Day 56 (±3 days), whichever occurs first:

- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology. If an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;

On the day the bone marrow aspirate specimen is collected:

- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Assess the subject for relapse based on the local laboratory results (see criteria in Section 7.2).

6.2.2.2. Allogeneic Hematopoietic Stem Cell Transplantation (up to 180 Days After Transplant Date)

Subjects are permitted to undergo **allogeneic** HSCT after CR or CRi is achieved. Allogeneic HSCT for consolidation may be performed after the Induction Phase, anytime during the Consolidation Phase or, if certain criteria are met (see below), within the first 3 months of the Continuation Phase. Refer to the schedule of events for the list of assessments and procedures to be performed after allogeneic HSCT (Table 17.5).

Quizartinib/placebo should be discontinued at least 7 days before the start of a conditioning regimen.

Following the allogeneic HSCT, the investigator will collect the following information from the transplant unit:

- Karnofsky performance status prior to the start of the conditioning regimen;

- All conditioning regimens the subject has received;
- The date and type of transplant the subject has received;
- The type of donor.

Additionally, from the time of allogeneic HSCT up through the end of the allogeneic HSCT period (up to 180 days after the date of transplant), the investigator will collect the following information from the transplant unit every 4 weeks:

- Determine if the subject has experienced a relapse, based on the available bone marrow aspirate and/or biopsy pathology report. Collect a copy of de-identified local pathology report from the bone marrow aspirate for submission to IRC;
- Review and document the development of acute and chronic GVHD;
- Record all engraftment failures;
- Record all transplant related mortality and death for any reason.

In addition to the above every 4-week follow-up for GVHD following the allogeneic HSCT, additional information regarding GVHD (Table 17.16, Table 17.17 and Table 17.18), will be collected at the following post-HSCT timepoints: Day 100, 6 months (± 3 months), 12 months (± 3 months), 18 months (± 3 months), and 24 months (- 3/+ 6 months).[43,44]

Once the subject is able, the subject will return to the clinic for site visits every 4 weeks (see Section 6.2.2.2.1).

A subject is permitted to undergo allogeneic HSCT for consolidation after the start of the Continuation Phase if the following criteria are met:

- When the subject starts the Consolidation Phase, the plan is for the subject to undergo HSCT as part of consolidation therapy;
- A donor is not able to be found during the Consolidation Phase but becomes available after the start of the Continuation Phase;
- The investigator discusses the case with the Medical Monitor;
- Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results;
- The transplant is performed within 3 months after Day 1 of continuation therapy.

For subjects who have an allogeneic HSCT for consolidation within the first 3 months of continuation therapy, subjects restart therapy at the cycle they should have been in, had they not stopped; eg, if the subject stopped at end of Cycle 2, and were ready to resume therapy 12 weeks later (with 28 days per cycle), then the restart cycle would be Cycle 3.

Any HSCT performed for other reasons, eg, molecular relapse, will be considered nonprotocol-specified AML therapy, and the subject will be discontinued from quizartinib/placebo but will continue to be followed for outcome data.

Subjects are **not** permitted to undergo autologous HSCT at any time during the study. Subjects who undergo autologous HSCT will be discontinued from quizartinib/placebo but will continue

to be followed for outcome data. In addition, the date and type of the transplant, and transplant related mortality and death for any reason will be recorded.

6.2.2.2.1. Post-Allogeneic HSCT Visits (up to 180 Days After Transplant Date)

This Section describes visits for subjects who have undergone allogeneic HSCT and who are able to return to the site for visits, but do not yet meet the eligibility criteria for the Continuation Phase (See Section 4.1.3). Visits will be conducted every 4 weeks.

The following activities will take place during these visits:

- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology (verify peripheral smear is not abnormal and cytopenias do not develop);
- If peripheral smear is abnormal or cytopenias develop, per hematology results, then collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Evaluate if the subject is eligible for the Continuation Phase;
- Assess the subject for relapse based on the local laboratory results (see Section 7.2);
- Review and document all concomitant medications and transfusions the subject has received since the subject resumed study visits;

The following will take place every 12 weeks:

- Collect a bone marrow aspirate for laboratory analysis and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse (see Section 7.2).

6.2.3. Continuation Phase (up to 36 cycles)

Following consolidation therapy, subjects will enter the Continuation Phase if they meet the inclusion criteria (see Section 4.1.3 Inclusion Criteria – Continuation Phase). In addition, per investigator discretion, subjects who have achieved CR or CRi following Induction but are unable to receive consolidation therapy will be permitted to enter the Continuation Phase if they meet the inclusion criteria (see Section 4.1.3).

Subjects will receive quizartinib/placebo for up to 36 cycles (28 days per cycle), with no breaks in dosing between cycles. If quizartinib/placebo is interrupted, missed doses will not be made up.

Visits will be conducted at the following times:

- Cycle 1: Days 1, 8, and 15;
- Cycle 2: Days 1 and 15;
- Cycles 3 through 36: Day 1.

Refer to the schedule of events for the list of assessments and procedures to be performed during the Continuation Phase (Table 17.6).

During the Continuation Phase, EORTC QLQ-C30 and EQ-5D-5L assessments will be administered every 3 cycles up through Cycle 36 at the following visits:

- Cycle 1, Day 1
- Cycle 4, Day 1;
- Cycle 7, Day 1;
- Cycle 10, Day 1;
- Cycle 13, Day 1;
- Cycle 16, Day 1;
- Cycle 19, Day 1;
- Cycle 22, Day 1;
- Cycle 25, Day 1;
- Cycle 28, Day 1;
- Cycle 31, Day 1;
- Cycle 34, Day 1;
- Cycle 36, Day 28 (End of Treatment [EOT]).

During the Continuation Phase, a bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected at the following visits:

- Cycle 1, Day 1
- Cycle 4, Day 1 (12 weeks);
- Cycle 7, Day 1 (24 weeks);
- Cycle 10, Day 1 (36 weeks);
- Cycle 13, Day 1 (48 weeks);
- Cycle 19, Day 1 (72 weeks);
- Cycle 25, Day 1 (96 weeks).

An aspirate specimen (or core biopsy specimen if adequate aspirate specimen not available) from all protocol-specified bone marrow procedures will be sent to both the local and central laboratories for assessment of morphology. In addition, if an unscheduled bone marrow

examination is performed, an aspirate specimen will be sent to both the local and central laboratories for assessment and a blood sample should be obtained for local hematology.

At any time during the Continuation Phase, if relapse is suspected based on abnormal peripheral smears or development of cytopenias, collect a bone marrow aspirate specimen for laboratory analysis and document results; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected. If a bone marrow aspirate specimen cannot be collected, then peripheral blood phenotyping should be performed to confirm that blasts are leukemic. Follow-up hematology should be performed after phenotyping.

6.2.3.1. Continuation Therapy

6.2.3.1.1. Cycle 1, Day 1

The following activities and/or assessments will be performed on Cycle 1, Day 1, prior to quizartinib/placebo administration, unless otherwise noted:

- Confirm that the subject meets all of the inclusion criteria for the Continuation Phase (see Section 4.1.3);
- For subjects who underwent allogeneic HSCT, collect updated medical history , including clinically relevant medical conditions that had onset and resolved during HSCT period as well as any medical condition with onset during the HSCT period and still ongoing on Day 1 of Continuation (see Section 9.1 for recording AEs during HSCT);
- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Conduct a physical examination (Section 9.10), including an evaluation for signs and symptoms of relapse;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight;
- Assess and record the subject's ECOG performance status;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test before study drug administration and document the results; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot

be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories. If the last aspirate/biopsy during the Consolidation Phase was done ≤7 days prior to Day 1 then collection of the aspirate specimen or core biopsy specimen does not need to be repeated;

  - Collect a copy of de-identified local pathology report for submission to IRC;

- Assess the subject for relapse based upon the local laboratory results (see Section 7.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit. Counsel the subject on the dosing regimen, from Days 1 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day;
- Administer the first dose of quizartinib/placebo.
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.13). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.3;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;

6.2.3.1.2. Cycle 1, Day 8 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 8:

- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Assess the subject for relapse (see Section 7.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Counsel the subject on the quizartinib/placebo dosing regimen from Days 9 through 14, including the total number of tablets to be taken daily, and confirm the subject's

understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 15;

- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.13). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.3;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;

6.2.3.1.3. Cycle 1, Day 15 (±1 Day)

The following activities and/or assessments will be performed on Cycle 1, Day 15:

- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology (can be done monthly after blood counts recovery);
  - Chemistry;
- Assess the subject for relapse (see Section 7.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance;
- If the average QTcF of the triplicate ECGs is ≤450 ms on Cycle 1, Day 15, increase the dose of quizartinib/placebo for the rest of the Continuation Phase starting on Day 16, as described in Section 5.4.3;
- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit and counsel the subject on the dosing regimen, from Days 16 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind

subjects that the dose of quizartinib/placebo will be administered at the study site on Cycle 2, Day 1;

- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.13). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.3;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;

6.2.3.1.4. Cycle 2, Day 1 (±1 Day)

The following activities and/or assessments will be performed on Cycle 2, Day 1:

- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Assess the subject for relapse (see Section 7.2);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance;
- If the dose of quizartinib/placebo was not increased on Cycle 1, Day 16, increase the dose of quizartinib/placebo for the rest of the Continuation Phase starting on Cycle 2, Day 2 if the average QTcF of the triplicate ECG is ≤450 ms on Cycle 2, Day 1.

- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit and counsel the subject on the dosing regimen, from Days 2 through 14, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day. Remind subjects that the dose of quizartinib/placebo will be administered at the study site on Day 15;
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.
- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.13). After subjects have been fully supine for 10 minutes, record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.3;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;

6.2.3.1.5. Cycle 2, Day 15 (±1 Day)

The following activities and/or assessments will be performed on Cycle 2, Day 15:

- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology (can be done monthly after blood counts recovery);
  - Chemistry;
- Assess the subject for relapse (see Section 7.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Counsel the subject on the quizartinib/placebo dosing regimen, from Days 16 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day.
- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

- Perform triplicate 12-lead ECG 2 to 4 hours postdose (Table 17.13). After subjects have been fully supine for 10 minutes record the first of the triplicate ECGs. Triplicate ECGs must be obtained at least 1 minute apart;
- Collect a blood sample for sparse PK sampling within 10 minutes after the last triplicate ECG, see further details in Table 8.3;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay 2 to 4 hours postdose (Table 8.5), immediately after PK sample collection;

6.2.3.1.6. Cycle 3, Day 1 (±3 Days)

The following activities and/or assessments will be performed on Cycle 3, Day 1:

- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Perform triplicate 12-lead ECG, fully supine for 10 minutes before the ECG (Table 17.13);
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Assess the subject for relapse (see Section 7.2);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance
- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit and counsel the subject on the dosing regimen, from Days 1 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day.

- Administer quizartinib/placebo. The dose may be given with or without food. It is recommended that the dose be given at the same time every day.

6.2.3.1.7. Cycle 4, Day 1 and Day 1 of Cycle 7, Cycle 10, Cycle 13, Cycle 19, and Cycle 25 (±3 Days)

The following activities and/or assessments will be performed:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Perform triplicate 12-lead ECG, fully supine for 10 minutes before the ECG;
- If subject is included in the PK-ECG-Biomarker Substudy (n = up to 100 subjects):
  - Collect blood samples for the PIA assay anytime postdose (Table 8.5);
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Collect a bone marrow aspirate specimen (per schedule in Section 6.2.3) and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate specimen cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance;

- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit and counsel the subject on the dosing regimen, from Days 1 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day.

6.2.3.1.8. All Other Subsequent Cycles, Day 1 (±3 Days)

The following activities and/or assessments will be performed on Day 1 of each subsequent cycle, unless otherwise specified. This section covers visits where a bone marrow assessment is not being performed, from Cycle 5, Day 1 through Cycle 36, Day 1.

- On Cycle 16, Day 1; Cycle 22, Day 1; Cycle 28, Day 1; Cycle 31, Day 1; and Cycle 34, Day 1: administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Conduct a physical examination (Section 9.10), including an evaluation of the subject for signs and symptoms of relapse;
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Record triplicate 12-lead ECG, fully supine for 10 minutes before the ECG;
- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving quizartinib/placebo (refer to Section 9.6);
- Assess the subject for relapse (see Section 7.2);
- Record all healthcare resource utilization since the last visit (see Section 10.2);
- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance;
- Dispense a sufficient quantity of quizartinib/placebo to supply the subject until the next scheduled visit and counsel the subject on the dosing regimen, from Days 1 through 28, including the total number of tablets to be taken daily, and confirm the subject's understanding. Counsel subjects that quizartinib/placebo may be taken with or without food and should be taken at about the same time every day.
- On Cycle 36, Day 1, remind subjects to stop taking quizartinib/placebo on Day 28.

6.2.3.2. Allogeneic Hematopoietic Stem Cell Transplantation

Refer to Section 3.2.2.2.1 for subjects who are being considered for allogeneic stem cell transplantation during the Continuation Phase.

6.3. End of Treatment (+ 7 Days)

The end of treatment visit is for subjects who complete 36 cycles of continuation therapy or who permanently discontinue quizartinib/placebo early.

Subjects who permanently discontinued quizartinib/placebo because they completed 12 cycles of continuation therapy (under Protocol Version 1.0 or 2.0), were restarted on quizartinib/placebo and have now completed 36 cycles will need to complete an additional End of Treatment Visit once they have permanently discontinued study drug for the second and last time.

The end of treatment visit should occur within 7 days after the last dose of quizartinib/placebo or at the time the decision to discontinue quizartinib/placebo is made, if this is greater than 7 days after the last quizartinib/placebo treatment, unless there is a medical condition that prevents subjects from completing the visit within this time. Subjects must complete all end of treatment assessments as well as their regularly scheduled evaluations if they are discontinuing during a scheduled visit. The following activities will take place during this visit:

- Administer the EORTC QLQ-C30 and EQ-5D-5L assessments before any other assessments or procedures;
- Conduct a physical examination (Section 9.10);
- Record vital signs (blood pressure, pulse rate, respiratory rate, and temperature);
- Weight;
- Assess and record the subject's ECOG performance status;
- Perform triplicate 12-lead ECG, fully supine for 10 minutes before the ECG;
- Collect and send blood and urine samples to the laboratory for the following tests (Table 17.19):
  - Hematology;
  - Chemistry;
  - Coagulation;
  - Urinalysis (only as needed; eg, if renal function has decreased);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 6 months of discontinuing quizartinib/placebo (refer to Section 9.6);
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2);
- Record all healthcare resource utilization since the last visit (see Section 10.2);

- Review and document all concomitant medications and transfusions the subject has received;
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Collect quizartinib/placebo bottles returned by subjects and assess treatment compliance, if subject is outpatient.

6.4. Long-Term Follow-up Phase

The Long-Term Follow-up Phase begins upon completion of 36 cycles of quizartinib/placebo in the Continuation Phase or permanent discontinuation of quizartinib/placebo in any phase. Refer to the schedule of events for the list of assessments and procedures to be performed during the Long-Term Follow-up Phase (Table 17.7).

6.4.1. Safety Follow-up Visit

The Safety Follow-up Visit should occur 30 days (+ 7 days) after the last dose of quizartinib/placebo, once a subject permanently discontinues or completes the study. Telephone contact with the subject is sufficient unless: the subject has not had an EFS Event or any assessment must be repeated for resolution of treatment-related AEs. The following activities will take place during this visit:

- Assess the subject for relapse (see Section 7.2);
- For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test; subjects must have a negative result. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 6 months of discontinuing the quizartinib/placebo (refer to Section 9.6);
- Record all AEs experienced by the subject since the last evaluation:
  - Record any treatments (drug and nondrug) given for AEs;
- Record subsequent anti-leukemic treatments and their outcomes.

6.4.2. Long-Term Follow-up Visits

After completion of the Safety Follow-up Visit, the Long-Term Follow-up Visits will be performed as follows:

- Every 4 weeks for subjects who have **not** had an EFS event;
- Every 12 weeks for subjects who have had an EFS event.

If direct contacts are not possible due to withdrawal of consent or the subject becomes lost to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws. See Section 5.9.2.1 for further details on how subjects will be followed for vital status if they withdraw consent.

For women of childbearing potential (as defined in Section 4.1.1): perform a urine or serum pregnancy test 6 months after the last dose of investigational drug or cytarabine, whichever is

later. Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 6 months of discontinuing quizartinib/placebo (refer to Section 9.6).

All subjects will be followed for survival and subsequent anticancer therapy, if available.

6.4.2.1. Long-Term Follow-up Visits for Subjects Who Have Not Had an EFS Event (Refractory/Relapse)

Subjects who have **not** had an EFS event will be followed every 4 weeks for relapse and survival status.

The following activities will be done every 4 weeks:

- Collect and send blood samples to the laboratory for the following tests (Table 17.19):
  - Hematology (verify peripheral smear is not abnormal and cytopenias do not develop);
  - If peripheral smear is abnormal or cytopenias develop, per hematology results, then collect a bone marrow aspirate specimen and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate sample cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2);
- Record subsequent anti-leukemic treatments and their outcomes.

6.4.2.1.1. Bone Marrow Specimen Collection

A bone marrow aspirate specimen (or a core biopsy specimen if aspirate cannot be obtained) will be collected as noted below, until relapse or 96 weeks have passed, whichever occurs first.

For subjects who permanently discontinue quizartinib/placebo prior to starting continuation therapy and who **have not** undergone HSCT:

- Collect a bone marrow aspirate specimen at the end of 12 weeks, 24 weeks, 36 weeks, 48 weeks, 72 weeks, and 96 weeks from the date of discontinuation of quizartinib/placebo and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate sample cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories.
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2).

For subjects who permanently discontinue quizartinib/placebo prior to starting continuation therapy and who **have** undergone HSCT:

- Collect a bone marrow aspirate specimen during the first site visit following HSCT;
  - If an aspirate/core biopsy specimen was obtained ≤14 days prior to the first site visit following HSCT and the specimen is sent to both the local and central laboratories, then collection does not need to be repeated at the first site visit following HSCT;
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2).
- Collect a bone marrow aspirate specimen at the end of 12 weeks, 24 weeks, 36 weeks, 48 weeks, 72 weeks, and 96 weeks from the first site visit following HSCT and send to both the local and central laboratories for assessment of morphology; if an adequate aspirate sample cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories.
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2).

For subjects who permanently discontinue quizartinib/placebo at any time during the Continuation Phase:

- Continue to collect bone marrow aspirate specimens at the end of 12 weeks, 24 weeks, 36 weeks, 48 weeks, 72 weeks and 96 weeks from Cycle 1, Day 1 of the Continuation Phase. Send to both the local and central laboratories for assessment of morphology; if an adequate aspirate sample cannot be collected, a core biopsy specimen will be collected and sent to both the local and central laboratories.
  - Collect a copy of de-identified local pathology report for submission to IRC;
- Assess the subject for relapse based upon the local laboratory results (see Section 7.2).

For subjects who completed 36 cycles of continuation therapy:

- Assess the subject for relapse based upon the local laboratory results (see Section 7.2).

6.4.2.2. Long-Term Follow-up Visits for Subjects Who Have Had an EFS Event (Refractory/Relapse)

Subjects who have had an EFS event will be followed every 12 weeks for survival status.

The following activities will take place during long-term follow-up:

- Record subsequent anti-leukemic treatments. Record outcomes and remission status following subsequent anti-leukemic treatment, if available.
- Record survival, evaluated by telephone contact.

7. EFFICACY ASSESSMENTS

7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is OS.

Overall survival is defined as the time from Randomization until death from any cause. Subjects alive or lost to follow-up at the time of analysis will be considered censored at the date when they were last known to be alive.

7.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints (ie, secondary outcome measures) are:

- Event-free survival, which is defined as the time from Randomization until the date of the earliest of any of the following (refer to Table 17.15 for definition of response):
  - Refractory disease (or treatment failure) is determined at the end of the Induction Phase and defined as:
    - CR or CRi never achieved in the Induction Phase; or
    - Blasts <5% if Auer-rod positive; or
    - Appearance of new or worsening extramedullary disease;
    - For refractory disease, the EFS event date will be set to Day 1 at Randomization
  - Relapse after CR or CRi, which is defined as:
    - ≥5% blasts in the bone marrow aspirate and/or biopsy not attributable to any other cause; or
    - Reappearance of leukemic blasts in the peripheral blood; and/or
    - New appearance of extramedullary leukemia; or
    - Presence of Auer rods
  - Death from any cause at any time during the study.
- Composite CR rate which is the percentage of subjects achieving CR or CRi after Induction;
- Percentage of subjects achieving CRc with FLT3-ITD MRD negativity below a certain cutoff after Induction. Minimal or measurable residual disease is the presence of a small number of leukemic cells in the bone marrow of patients with AML below the level of detection using conventional morphologic assessment. The FLT3-ITD MRD assay by Next Generation Sequencing will be used to detect and quantify residual FLT3-ITD mutations;
- Complete remission rate, which is the percentage of subjects achieving CR after Induction;

- Percentage of subjects achieving CR with FLT3-ITD MRD negativity following induction therapy.

7.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are:

- Relapse-free survival (RFS) is the time from randomization, for subjects who achieve CR or CRi in the Induction Phase, until documented relapse or death from any cause, whichever comes first. Subjects alive without relapse or lost to follow-up at the time of analysis will be considered censored at the date of their last response/relapse assessment;
- Duration of CR is the time from the first documented CR until documented relapse or death from any cause, whichever comes first. Subjects alive without relapse or lost to follow-up as of the time of analysis will be censored at the date of their last response/relapse assessment;
- Complete remission rate at the end of the first Induction cycle is the percentage of subjects who achieved CR after 1 Cycle of Induction;
- Composite CR rate at the end of the first Induction cycle is the percentage of subjects whose best response is CR or CRi at the end of first Induction cycle;
- CRh rate is the percentage of subjects achieving CRh after Induction (only for IRC assessment of response);
- MLFS rate is the percentage of subjects achieving MLFS after Induction (only for IRC assessment of response);
- RFS in subjects who enter the Continuation Phase is the time from randomization, for subjects who achieve CR or CRi in the Induction Phase, until relapse or death from any cause, whichever comes first;
- Transplantation rate is the percentage of subjects undergoing allogeneic HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens);
- Subject reported QoL and symptoms as assessed with the EORTC QLQ-C30 Questionnaire;
- General health status assessed using EuroQol (EQ-5D-5L) Questionnaire;
- Healthcare resource utilization.

7.4. Appropriateness of Selected Efficacy Endpoints

The initial goal of therapy for AML is to achieve a CR, given that a CR with currently available therapy is requisite, although not sufficient, for a cure. Complete remission is the most important initial response reported in Phase 3 trials because it is the sole outcome currently associated with improved survival. The goal of treatment in AML is to reduce the blasts in the bone marrow to below 5% (CR) and return the blood cell counts to normal levels.

After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia or thrombocytopenia (CRi). The outcome for these patients does not seem to be comparable to that of patients with normalization of all counts, especially for those patients during initial therapy for their AML. This category of response indicates activity of the investigational agent. Patients in CRi might be considered for the transplant.[45]

Improvement in EFS has been shown to correlate with increased OS in newly-diagnosed AML patients undergoing induction treatment and for AML patients in remission with maintenance therapy. Data from the ECOG E1900 trial, presented at the 2014 American Society of Hematology meeting, showed concordance between EFS and OS.[46] This randomized, Phase 3 trial enrolled 657 subjects, 16 to 60 years old, with newly–diagnosed AML. Subjects were randomized to receive daunorubicin 45 mg/m^2 or 90 mg/m^2 in combination with cytarabine followed by consolidation therapy.

An increase in EFS, which comprises an increased rate of remission, an increased duration of remission, or a reduction in early deaths or deaths during remission, is a benefit. Therefore, EFS represents a clinically relevant end point because relapse or treatment failure in AML signifies a reduced quality of life and substantial morbidity or mortality resulting either from the use of toxic salvage therapies, progressive disease, or both. For patients with AML who achieve CR after induction and consolidation therapy, delaying or preventing relapse is critical to long-term survival or cure.[47]

Overall survival is precise and easy to measure. Demonstration of a statistically significant improvement in OS can be considered to be clinically significant if the toxicity profile is acceptable. Difficulties in performing and analyzing survival studies include long follow-up periods in large trials and subsequent cancer therapy potentially confounding survival analysis.[48]

Health-related quality of life (HRQoL) assessment in cancer research has become critical to fully evaluate overall treatment effectiveness by also formally including the patient's perspective as an important objective.

The assessment of patient-reported outcomes (PROs), including HRQoL has become critical to fully evaluate overall treatment effectiveness through incorporation of the patient's perspective. Major cancer societies have been supporting its use as a key outcome for more than 2 decades. Acute leukemia patients experience significant symptom burden and detrimental impact on domains of HRQoL, including physical and emotional well-being, especially in the early course of disease. Intensive therapy may also detrimentally affect PROs. Fatigue is a particularly intense symptom and is significantly inversely correlated with physical and emotional functioning.[45,49, 50, 51] Accordingly, patient reported symptoms and HRQoL are assessments of clinical benefit in acute leukemia.[52]

European Organisation for Research and Treatment of Cancer QLQ-C30 is a questionnaire developed to assess the QoL of cancer patients, which has been widely used in cancer (including leukemia) clinical trials.[53] It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a number of single items assessing additional symptoms commonly reported by cancer patients (constipation, diarrhea, sleep and dyspnea), perceived financial impact of the disease and a global health status/QoL scale.

7.5. Independent Review Committee

An IRC (Section 15.10) will independently review the following events in a blinded manner and without any knowledge of the subject's randomized treatment assignment:

- During the Induction Phase, the IRC will independently assess the response for each bone marrow aspirate (or biopsy, if applicable) sample collected, regardless of whether it is the first or second cycle. If no blood counts are available on the day of the bone marrow specimen collection or if blood counts have not recovered on the day of the bone marrow specimen collection, blood counts within ± 14 days of the bone marrow specimen collection will be used to assess response.
- During the post-Induction Phases the IRC will independently review data to assess for relapse.

Details about the definitions of the endpoints and IRC processes will be described in the IRC charter.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Endpoint(s)

Blood samples for PK assessments will be collected at multiple time points in the study, as outlined in Table 8.1, Table 8.2, Table 8.3, and Table 8.4. Details for blood sampling, processing, storage, and shipment for PK samples will be provided in the study laboratory manual.

8.1.1. Sparse PK Sampling (Induction, Consolidation, and Continuation Phases)

During the Induction Phase (non-PK-ECG-Biomarker Substudy subjects only), blood should be collected for plasma quizartinib PK on Cycle 1; -0.5 to 0 hours (predose) on Day 8 and 2 to 4 hours (postdose) on Day 8, Day 15, and Day 21 per Section 6.2.1 and Table 8.1 within 10 minutes after the ECG is performed.

During the Consolidation Phase (all subjects), blood should be collected for plasma quizartinib PK on Cycle 1; -0.5 to 0 hours (predose) on Day 6 and 2 to 4 hours (postdose) on Day 6, Day 13, and Day 19 per Section 6.2.2 and Table 8.2 within 10 minutes after the ECG is performed.

During the Continuation Phase (all subjects), blood should be collected for plasma quizartinib PK 2 to 4 hours postdose of quizartinib/placebo on Cycle 1; Day 1, Day 8, and Day 15, and Cycle 2; Day 1 and Day 15 per Section 6.2.3 and Table 8.3 within 10 minutes after the ECG is performed.

The exact time of each ECG and its corresponding PK sample collection will be recorded. See Appendix 17.5.2 for ECG collection timing.

Table 8.1: Sparse PK Sampling for Quizartinib and its Metabolite (AC886) During Induction – Cycle 1 (All Subjects Not in the PK-ECG-Biomarker Substudy)

Induction Phase		
Cycle 1		
Day 8	Day 15	Day 21
PK[a]	PK[a]	PK[a]

ECG = electrocardiogram; PK = pharmacokinetics
[a] Within 10 minutes after the ECG, -0.5 to 0 hours (predose) Day 8 and 2 to 4 hours (postdose) Day 8, Day 15, and Day 21.

Table 8.2: Sparse PK Sampling for Quizartinib and its Metabolite (AC886) During Consolidation – Cycle 1 (All Subjects)

Consolidation Phase		
Cycle 1		
Day 6	Day 13	Day 19
PK[a]	PK[a]	PK[a]

ECG = electrocardiogram; PK = pharmacokinetics
[a] Within 10 minutes after the ECG, -0.5 to 0 hours (predose) on Day 6 and 2 to 4 hours (postdose) on Day 6, Day 13, and Day 19.

Table 8.3: Sparse PK Sampling for Quizartinib and its Metabolite (AC886) During Continuation – Cycles 1 and 2 (All Subjects)

Continuation Phase				
Cycle 1			**Cycle 2**	
Day 1	Day 8	Day 15	Day 1	Day 15
PK[a]	PK[a]	PK[a]	PK[a]	PK[a]

ECG = electrocardiogram; PK = pharmacokinetics
[a] Within 10 minutes after the ECG, which is performed 2 to 4 hours postdose.

Blood sampling, processing, storage, and shipment instructions are provided in the laboratory manual. Plasma quizartinib and its metabolite (AC886) will be analyzed using validated liquid chromatography-tandem mass spectrometry methods.

8.1.2. PK-ECG-Biomarker Substudy (Induction Phase)

Up to 100 subjects who consent to participation will have intense PK sampling for plasma quizartinib concentrations and its metabolite (AC886) at Cycle 1 during the Induction Phase on Day 8, Day 15, and Day 21 as shown in Table 8.4, within 10 minutes after the ECG is performed. This will be referred as the "PK-ECG-Biomarker Substudy". The predose sample should be collected within 0.5 to 0 hours prior to dose. The 1, 2, 4, and 6 hour post dose samples should be taken within ±0.5 hour of nominal time. The 24 hour post dose samples should be taken within ±3 hours of nominal time and before administration of the next dose, when applicable.

Table 8.4: PK-ECG-Biomarker Substudy: PK Time Points for Quizartinib and its Metabolite (AC886) During the Induction Phase (Cycle 1 Only)

Induction Cycle 1												
Day 8 (First Day of Quizartinib Dosing)					**Day 9**	**Day 15**	**Day 21 (Last Day of Quizartinib Dosing)**					**Day 22**
Hour Predose	**Hour Postdose**						**Hour Predose**	**Hour Postdose**				
-0.5 to 0	1[a]	2[a]	4[a]	6[a]	24[b]	2 to 4	-0.5 to 0	1[a]	2[a]	4[a]	6[a]	24[c]

ECG = electrocardiogram; PK = pharmacokinetics
[a] ±0.5 hour of nominal time
[b] ±3 hours of nominal time and before administration of the next dose
[c] ±3 hours of nominal time

8.2. Pharmacodynamic Endpoint(s)

- Inhibition of FLT3-ITD activity in an ex vivo PIA assay

Up to 100 subjects who are participating in the PK-ECG-Biomarker Substudy will have plasma samples collected for testing in an ex vivo PIA assay. Samples for PIA assessment will be collected as described in Section 6.2.1.1, Section 6.2.2.1, Section 6.2.3, and Table 8.5. When collected on the same day as PK sample collection, PIA samples will be collected immediately after PK sample collection.

Table 8.5: PK-ECG-Biomarker Substudy: Time Points for PIA Samples

Phase	Induction				Consolidation			Continuation										
Cycle	1				1			1			2		4	7	10	13	19	25
Day	8[a]		15[a]	21[a]	6[a]	13[a]	19[a]	1	8[a]	15[a]	1	15[a]	1	1	1	1	1	1
Hours	-0.5 to 0	2	2 to 4	2	2 to 4			2 to 4			2 to 4		anytime postdose					

ECG = electrocardiogram; PIA = plasma inhibitory activity; PK = pharmacokinetics
[a] Collect PIA sample immediately after PK sample collection

8.3. Biomarker Endpoint(s)

In this study, biomarker analyses will be used to investigate the effect of quizartinib at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. The required sample collection information should be recorded on the electronic case report form (eCRF) page(s) and central laboratory requisition form(s). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the study laboratory manual.

- FLT3-ITD MRD by next generation sequencing will be used to detect and quantify residual FLT3 ITD mutations. (Results will not be available until the end of the study.)

  For subjects who are in CR or CRi, bone marrow samples from the following visits will be analyzed for FLT3-ITD MRD: Screening; End of Induction; Consolidation Last Cycle; Post–HSCT; Continuation Cycle 1, Day 1; Continuation Cycle 4, Day 1; and EOT (ie, completion of 36 cycles of continuation therapy or early permanent discontinuation of quizartinib/placebo).

- Mutations in the kinase and juxtamembrane domains of FLT3 and other somatic mutations known to be associated with AML or myeloid diseases (eg, CEBPA, DNMT3A, IDH1, IDH2, Kit, NPM1 and NRAS), determined with bone marrow or whole blood samples.

  Bone marrow samples from the following visits will be analyzed for somatic mutations: Screening; Continuation Cycle 4, Day 1; and at the time of relapse (as defined in Section 7.2).

- Pharmacodynamic biomarkers will be analyzed with the intent of monitoring the anti-tumor impact of treatment with quizartinib. The following candidate pharmacodynamic biomarkers are currently envisaged (other pharmacodynamic biomarkers in addition to or in place of these may be considered as suggested by updated literature): FLT ligand; allelic ratio of FLT3-ITD; and flow cytometer analysis by using CD33, CD34, CD38, or any other AML or blood cell markers. These pharmacodynamic biomarkers will be assessed in bone marrow, blood, RNA, or DNA that is left over from samples collected for other tests as described in Table 17.1, Table 17.2, Table 17.3, and Table 17.4 using validated assays. One or more of the aforementioned pharmacodynamic biomarkers may also be explored for predictive value.

- Biomarker samples will be shipped to a central laboratory. Sample collection, preparation, handling, storage, and shipping instructions are provided in the study laboratory manual.
- During the study, in addition to the biomarkers specified above, exploratory research may be conducted on any tumor sample. These studies would extend the search for other potential biomarkers relevant to the effects of quizartinib, cancer and/or the resistance to treatment. This may include the development of ways to detect, monitor, or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability.

  If the subject agrees, the remaining biomarker samples (bone marrow, blood, or other specimens obtained during the study) may be stored for up to 15 years and further analyzed to address scientific questions related to quizartinib and/or AML.

These assessments will be performed as described in Section 6, Table 17.1, Table 17.2, Table 17.3, Table 17.4, and Table 17.6.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

8.5.1. Genomic or Genetic Analysis

Blood and epithelial oral cell samples will be collected for pharmacogenetic sample banking from subjects who have provided a separate informed consent for this part of the study. Participation in this part of the study is optional for all subjects. For those subjects who choose to participate, samples will be banked for possible future pharmacogenetic and DNA analysis. These samples may be analyzed only for genes suspected to contribute to the safety and efficacy of the study medications.

Samples will be retained until the genetic material has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the genetic samples will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

For instructions on management of pharmacogenomics samples please refer to the study laboratory manual.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

From the initial ICF (FLT3-ITD Screening or Main Study) being signed and up to Randomization (Induction phase, Cycle 1 Day 7), all SAEs considered related to study procedures by the investigator will be recorded. For randomized subjects, AEs and SAEs occurring between Induction Phase Cycle 1 Day 1 and Day 6 will be recorded retrospectively. From Randomization and up to the 30-Day Safety Follow-up Visit, all AEs (see Section 9.3.1 for definitions) observed by the investigator or reported by the subject will be recorded, except during allogeneic HSCT (see Section 6.2.2.2). Medical conditions (including clinically significant laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to initial ICF will be recorded as part of medical history. For subjects who undergo allogeneic HSCT, medical conditions (including clinically significant laboratory values/vital signs that are out of range) that were diagnosed or that occurred after allogeneic HSCT will be recorded as post-HSCT medical history. Any AEs that are unresolved at the time of transitioning to conditioning regimen for allogeneic HSCT should be followed up when the subject returns for Post-HSCT Visit (see Section 6.2.2.2.1).

All AEs, SAEs, and events of special interest are to be reported according to the procedures in Section 9.4.

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

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.3. The investigator's assessment must be clearly documented in the Study Center's source documentation with the investigator's signature.

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

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

Refractory disease and relapse (see Section 7.2 for criteria) are study endpoints and consequently, refractory disease, relapse, or worsening of AML should not be reported as an

AE/SAE. However, clinical events associated with refractory disease/relapse and its sequelae resulting in a serious outcome should be reported as AEs or SAEs. For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to quizartinib/placebo should also be reported and managed as an SAE.

The investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

9.2. Events of Special Interest

9.2.1. QTc Prolongation, Torsades de Pointes, and Other Ventricular Arrhythmias

Subjects who experience >480 ms QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved, as described in Section 5.6.1.1.

QTcF prolongation ≥ Grade 3, either serious or non-serious and whether or not causally related, must be recorded as AE or SAE in the Electronic Data Capture (EDC) system within 24 hours of awareness of the central ECG laboratory reading, with the investigator's assessment of seriousness, causality, and a detailed narrative.[54] The central ECG reading confirming QTcF prolongation ≥ Grade 3 is to be recorded in the EDC system.

9.2.2. Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥3 × ULN with simultaneous TBL ≥2 × ULN] should always be recorded as an AE or SAE within 24 hours of awareness, with the investigator's assessment of seriousness, causality, and a detailed narrative.[55]

Subjects will be monitored as described in Section 5.6.2.1.1.

9.3. Adverse Event

9.3.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[56]

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

9.3.2. Serious Adverse Event

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more.[56]

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

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

9.3.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the latest NCI CTCAE:[54]

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

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE

assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

9.3.4. Causality Assessment

The causal relationship to an AE/SAE will be assessed with consideration to quizartinib/placebo on the basis of the investigator's judgment and the following definitions. For SAEs only, the causal relationship to cytarabine and daunorubicin, if applicable, will also be assessed. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE/SAE follows a reasonable temporal sequence from quizartinib/placebo administration (or for SAEs only, from cytarabine or daunorubicin administration) and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

or

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

9.3.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in quizartinib/placebo dosage was made.
- Drug Withdrawn: The quizartinib/placebo was permanently stopped.
- Dose Reduced: The dosage of quizartinib/placebo was reduced.
- Drug Interrupted: The quizartinib/placebo was temporarily stopped.
- Dose Increased: The dosage of quizartinib/placebo was increased.
- Not Applicable: Subject died, quizartinib/placebo had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.3.6. Other Action Taken for Event

- None.
  - No treatment was required.

- Medication required.
  - Prescription and/or over-the-counter medication was required to treat the AE.
- Other.

9.3.7. Adverse Event Outcome

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

9.4. Safety Reporting –Procedure For Investigators

All AEs, including SAEs and Events of Special Interest, will be reported in the EDC.

The following types of events should be reported by the investigator in EDC within 24 hours of awareness:

- SAEs (see Section 9.3.2 for definition)
- QTcF prolongation ≥ Grade 3, either serious or non-serious and whether or not causally related (see Section 5.6.1 for additional monitoring details)
- Hepatic events meeting combination abnormalities [ALT or AST ≥3 × ULN with simultaneous TBL ≥2 × ULN] (potential Hy's Law case), both serious and non-serious and whether or not causally related (see Section 5.6.2.1 for additional monitoring details)

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the quizartinib/placebo. Serious events also must be reported with investigator's assessment of causality to cytarabine and daunorubicin, if applicable. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the

narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

See study reference materials for contact information for SAE reporting. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

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

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

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the quizartinib/placebo, unless delegated to Daiichi Sankyo, it is the investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's responsibility to report SUSARs to all Central ECs, and the investigator's responsibility to inform the local EC.

9.6. Exposure In Utero During Clinical Studies

Women of childbearing potential (as defined in Section 4.1.1) must have negative urine or serum pregnancy test results at times specified in the Schedule of Events (Appendix 17.1). If required by local regulations, additional pregnancy testing will be performed. Follicle stimulating hormone (FSH) may be determined as necessary to confirm postmenopausal status. Serum pregnancy tests and FSH will be performed at the local laboratory.

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 6 months of discontinuing the quizartinib/placebo.

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

9.7. Clinical Laboratory Evaluations

Clinical laboratory determinations for hematology, blood chemistry, coagulation, and urinalysis will be analyzed. See Table 17.19 for specific analytes.

9.8. Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be determined and recorded at the times specified in the study schedule (Appendix 17.1).

9.9. Electrocardiograms

Supine triplicate 12-lead ECGs will be obtained at the times specified in the Schedule of Events (Appendix 17.5.2). Additional ECGs may be obtained at the investigator's discretion. If an ECG is abnormal then a repeat triplicate ECG must be performed.

See Section 5.6.1.1 for management of subjects with QTc prolongation. See Section 5.6.4, Section 5.8.3, and Appendix 17.5.1 for ECG monitoring requirements for subject receiving a concomitant drug that prolongs QTc or is a CYP3A4 inhibitor.

9.10. Physical Examinations

A complete physical examination will be performed at Screening and at additional times specified in the Schedule of Events (Appendix 17.1). Whenever possible, the same individual will perform subsequent examinations to identify changes from baseline. Clinically significant changes from baseline must be reported as AEs.

Symptom-directed physical examinations performed during the treatment period will be based on the subject's medical history and AEs, and will include weight determination and a review of body systems. During the Continuation Phase, this will also include an evaluation of signs and symptoms of relapse.

9.11. Other Examinations

Not applicable.

10. OTHER ASSESSMENTS

10.1. Health Economics and Outcome Research

10.1.1. Patient-Reported Outcomes

Patient-reported outcomes will be assessed using EORTC QLQ–C30 (Appendix 17.13) and EQ-5D-5L (Appendix 17.14).

- EORTC QLQ–C30
  - EORTC QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a number of single items assessing additional symptoms commonly reported by cancer patients (constipation, diarrhea, sleep, and dyspnea), perceived financial impact of the disease and a global health status/QoL scale. All scores are scaled from 0 to 100, with higher scores representing better QoL and fewer symptoms.[53]
  - The QLQ-C30 is the most widely used questionnaire for cancer (including leukemia) patients in clinical trials in Europe, and is also used extensively in America and throughout the rest of the world.[53] The psychometric properties of the QLQ-C30 have been well established and the questionnaire was found to possess the required standards such as validity (measuring what it is intended to measure), reliability (measuring with sufficient precision) and sensitivity (ability to detect changes).[53] A 10-point difference in a QLQ-C30 domain score is generally considered clinically important.[57] It has been shown to be sensitive to change in patients undergoing cancer treatment (chemotherapy and/or radiotherapy).[58]
- EQ-5D-5L
  - General health status will be assessed using EQ-5D-5L. The EQ-5D-5L is a 6-item generic multi-attribute preference-based health status questionnaire that is easy to administer and takes only 1 to 2 minutes to complete. The questionnaire will be used to generate study-specific data for the calculation of quality-adjusted life years for economic evaluation.
  - The EQ-5D-5L is in two parts. The first part comprises five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each assessed by one item with 5 response options ranging from no problems through profound difficulties. Accordingly, 3125 (5×5×5×5×5) potential health profiles can be generated to which public preferences or utilities from published value sets are applied, ranging from negative values to 1 (perfect health).[59] The second part of the EQ-5D-5L is a Visual Analogue Scale on which subjects rate their current health, with 0 representing the "worst health you can imagine" and 100 the "best health you can imagine."

10.2. Health Economic Assessments

The following variables will be collected and recorded to assess healthcare resource utilization during the treatment period (excluding the allogeneic HSCT period, when the subject is unable to attend site visits):

- Hospitalizations;
- Emergency room visits;
- Skilled nursing facility care;
- Unscheduled clinic visits;
- Hospice care;
- Concomitant medications and procedures.

11. STATISTICAL METHODS

11.1. Analysis Sets

All relevant analyses sets are defined as below:

- Safety Analysis Set will include all subjects who received at least 1 dose of quizartinib/placebo.
- Intent-to-treat (ITT) Analysis Set will include all subjects who are randomized.
- Per-protocol Analysis Set (PPS) will include all subjects in the ITT Analysis Set who have no major protocol deviations that would affect assessment of efficacy endpoints.
- PK substudy Analysis Set will include all subjects in ITT Analysis Set who participated in the PK substudy and received at least 1 dose of quizartinib and had at least 1 PK sample.
- Pharmacodynamic Analysis Set will include all subjects in ITT Analysis Set who received at least 1 dose of quizartinib/placebo and had at least 1 predose and 1 postdose corresponding pharmacodynamic assessment.
- Biomarker Analysis Set will include all subjects in ITT Analysis Set who received at least 1 dose of quizartinib/placebo and had at least one corresponding biomarker assessment.
- EQ-5D-5L and EORTC QLQ-C30 Analysis Set. The EQ-5D-5L and EORTC QLQ-C30 Analysis Set will include all subjects in the ITT Analysis Set who complete the relevant EQ-5D-5L and EORTC QLQ-C30 assessment at Screening, at least partially in a manner that permits imputation of missing responses posttreatment.

11.2. General Statistical Considerations

The randomization will be stratified by geographical region (North America, Europe, and Asia/Other Regions), Age (<60 years old, ≥60 years old), and WBC count at the time of diagnosis of AML ($<40\times10^9$/L, $\geq40\times10^9$/L).

Summary statistics will be presented by treatment group. For continuous variables, number of available observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the number and percentage in each category will be displayed.

Efficacy analyses will be performed on the ITT Analysis Set and PPS. Safety analyses will be performed using the Safety Analysis Set. All other efficacy exploratory analyses will be performed based on ITT Analysis Set and availability of assessment.

The efficacy analyses will be performed according to the treatment groups assigned at Randomization. For safety analyses, subjects will be analyzed according to actual treatment received.

Assessments of change from baseline to post-baseline or the ratio of post-baseline to baseline will include only those subjects with both baseline and post-baseline measurements. Baseline

will be defined in the SAP. In general, missing or drop-out data will not be imputed for the purpose of data analysis.

11.3. Study Population Data

Subject disposition will be summarized by treatment group and in total for those defined selected Analysis Sets.

The demographic and baseline characteristics such as baseline ECOG disease status will be summarized descriptively by treatment group for the ITT, PPS, and Safety Analysis Sets.

Quizartinib/placebo exposure (amount and duration), average daily dose and relative dose intensity will be summarized using descriptive statistics by treatment group for the Safety Analysis Set.

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version and summarized by system organ class, preferred term, and presented by treatment group.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

11.4.1.1. Primary Efficacy Analyses

Overall survival is the primary efficacy endpoint for this study (see Section 7.1 for the definition of OS).

The primary analysis for OS will be based on the ITT Analysis Set. Comparison of distribution of OS between treatment groups will be made using a stratified log-rank test with the 3 stratification factors used at randomization at a 2-sided 5% significance level. The median OS will be calculated based on Kaplan-Meier estimates and the corresponding 95% CI will be calculated using the method provided by Brookmeyer and Crowley.[60] In addition, the stratified Cox proportional hazards regression model will be performed to estimate hazard ratio (HR) along with the 2-sided 95% CI, and SAS PROC LIFETEST and PROC PHREQ will be used in the analysis.[61]

11.4.1.2. Secondary Efficacy Analyses

The analysis for EFS will be based on the ITT Analysis Set. The distribution of EFS will be compared between the 2 treatment groups using a stratified log-rank test with the 3 stratification factors used in randomization. The distribution function of EFS will be estimated using the Kaplan-Meier method. The median EFS along with the 2-sided 95% CIs by Brookmeyer and Crowley will be presented by treatment group.[60] The stratified Cox proportional hazards regression model will be used to estimate the hazard ratio of EFS, along with the 2-sided 95% CI.

EFS will be analyzed based on the response assessment by the IRC. EFS will also be analyzed based on the investigator's response assessment as a sensitivity analysis.

The CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity will be summarized along with 95% CI using Clopper-Pearson's method.[62] Comparisons of CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity between treatment groups will be made using a Cochran-Mantel-Haenszel test with the 3 stratification factors used in randomization.

To control for the family-wise type I error rate for the primary and secondary efficacy endpoints, a serial hierarchically ordered gatekeeping strategy will be employed. The primary assessment of OS in the ITT Analysis Set will be evaluated first, and if significant at a 2-sided alpha of 0.05, a statistical evaluation of EFS by IRC, based on the EFS definition in the Guidances,[63,72] will be performed in the ITT Analysis Set. After EFS evaluation, the order of other secondary endpoints to be tested will be CR rate, rate of subjects achieving CR with FLT3-ITD MRD negativity, CRc rate, and rate of subjects achieving CRc with FLT3-ITD MRD negativity. Testing will stop once 1 test in the sequence fails to be statistically significant.

11.4.1.3. Exploratory Efficacy Analyses

Relapse-Free Survival will be analyzed by treatment group using the Kaplan-Meier method for subjects achieving CRc.

RFS in subjects who enter the Continuation Phase will be summarized similarly as RFS.

Duration of CR will be analyzed similarly as RFS.

Rate of allogeneic HSCT, rate of CR at end of first Induction cycle, rate of CRc at end of first Induction cycle, rate of CRh after Induction (IRC evaluation only), and rate of MLFS after Induction (IRC evaluation only) will be summarized by treatment group with point estimate and associated 2-sided 95% CI constructed using Clopper-Pearson's method.[62]

Confidence interval presented for exploratory endpoints are provided for summary purpose, not inference.

11.4.1.4. Sensitivity and Supplementary Analyses

The final set of sensitivity and supplementary analyses will be selected and specified in the SAP.

11.4.1.5. Subgroup Analyses

The primary and secondary efficacy endpoints, OS and EFS, will be also analyzed for the following subgroups in the ITT Analysis Set:

- By region: North America, Europe, Asia/Other Regions;
- By age: <60, 60 to 65, and ≥65years old;
- By WBC count at the time of diagnosis of AML ($<40\times10^9$/L, $\geq40\times10^9$/L);
- By sex: male and female;
- By choice of anthracycline: daunorubicin or idarubicin;
- By race: Caucasian, Black/African American, Asian, Other.

The same statistical method employed for the analysis of OS and EFS will be used for the planned sub-group analyses.

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

For the PK-ECG-Biomarker Substudy: pharmacokinetic parameters of quizartinib and its metabolites (AC886) will be estimated for subjects who have sufficient plasma concentrations available. Standard non-compartmental analysis will be estimated for subjects with sufficient intense PK data available for the following PK parameters: AUC_{0-24}, Cmax, Cmin, Tmax, and accumulation ratio and parent/metabolite ratio at Day 8 and Day 21 during Cycle 1 of Induction. Plasma concentrations and PK parameters will be summarized using descriptive statistics by treatment group and by treatment phase when appropriate.

Population PK analysis will be conducted to characterize the PK profiles of quizartinib and its metabolite (AC886) in the target patient population, including quantification of inter-individual variability and identification of potential significant covariates (ie, patients demographics and clinical factors) that may affect the PK of quizartinib and its metabolite. If necessary, PK data from this study will be pooled with those from other Phase 1 and 2 studies for the population PK modeling.

The potential relationships between quizartinib PK exposure versus QTcF or clinical response measures will be explored by both graphical and modeling approaches.

Details about the non-compartmental analysis, population PK modeling and exposure-response analysis will be provided in separate plans. The population PK and exposure-response analysis results will be reported separately. In addition, population PK and pharmacodynamic analyses may be performed prior to database lock by a third party, unblinded pharmacometrician, who will be firewalled from the study team in accordance with the details provided in a separate document.

11.4.2.2. Pharmacodynamic Analyses

Number and percentage of subjects achieving full inhibition as measured by PIA will be summarized for each time point by treatment groups. A subject is said to have achieved full inhibition at a certain PIA assessment visit if the corresponding PIA value is >90%. Number and percentage of subjects achieving full inhibition will be provided for the quizartinib group. Summary statistics will be provided for the quizartinib group in the Pharmacodynamic Analysis Set.

11.4.2.3. Biomarker Analyses

Number and percentage of subjects expressing different AML associated mutations will be summarized by treatment group.

FLT3-ITD allelic ratio will be summarized and presented by treatment groups.

11.4.3. Safety Analyses

All safety analyses will be based on the Safety Analysis Set. Listings will be based on the Safety Analysis Set.

For each safety analysis, baseline will be defined in the SAP. No inferential statistical analysis is planned for safety data, unless otherwise specified. If the number of subjects with available data does not allow for the reliable estimation of variability at a scheduled time point, no summary statistics will be presented for that time point, unless otherwise indicated.

11.4.3.1. Adverse Event Analyses

Adverse events to be included in summary tables will be restricted to TEAEs. A TEAE is defined as an AE that occur, having been absent before first dose of quizartinib/placebo, or have worsened in severity after initiating quizartinib/placebo. Safety analyses include frequency and severity of TEAEs.

AEs collected more than **30** days after the last dose of quizartinib/placebo will not be considered TEAEs unless they are considered drug-related. If the relationship to drug is missing, the AE is considered drug-related.

AEs will be coded using MedDRA (the latest version) and assigned grades based on NCI CTCAE, Version 4.03. The number and percentage of subjects reporting TEAEs will be tabulated by the worst CTCAE grade, system organ class, and preferred term, with a breakdown by treatment group. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated by treatment group, as well as TEAEs/SAEs considered related to quizartinib/placebo and TEAEs leading to discontinuation of quizartinib/placebo, respectively.

A by-subject AE (including treatment emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, CTCAE grade, and relationship to quizartinib/placebo will be provided. Deaths, other SAEs, AESIs and other significant AEs, including those leading to permanent discontinuation from quizartinib/placebo, will be listed. The AESIs will be re-evaluated periodically and the final list of AESIs will be reflected in the final SAP.

SAEs and nonserious AESIs will be reconciled between the clinical and safety databases. The clinical database will be used to summarize and list the SAEs.

Subgroup analyses of AEs will be performed if applicable using subgroups defined in the SAP.

11.4.3.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment group including end of treatment visit as well as for the maximum and minimum post-baseline values.

Abnormal clinical laboratory results will be graded according to NCI CTCAE Version 4.03, if applicable. A shift table, presenting by treatment group the 2-way frequency tabulation for baseline and the worst post-baseline value according to the CTCAE grade, will be provided for

clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.4.3.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment group including end of treatment visit as well as for the maximum and minimum post-baseline values.

11.4.3.4. Electrocardiogram Analyses

Electrocardiogram parameters (PR, RR, QRS, QT, and QTcF) will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by treatment group by scheduled time of evaluation including end of treatment visit as well as for the maximum post-baseline values. QTcF will be considered as the primary correction method to assess QTc interval.

The number and percentage of subjects with QT/QTc interval values meeting the criteria will be tabulated (eg, QTcF ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) and QTcF maximum changes from baseline (>30 and >60 ms) over all post-treatment evaluations will be summarized. Electrocardiogram data will also be presented in the data listings.

11.4.3.5. Transfusion

Blood transfusion data will be summarized by treatment group and treatment phases.

11.4.3.6. Physical Examination Analyses

Physical examination findings will be listed for the Safety Analysis Set.

11.4.3.7. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization drug dictionary (WHODD) (most recent version). Number and percentage of subjects taking concomitant medications will be summarized by ATC2 class and preferred term and presented by treatment group.

11.4.3.8. Safety Subgroup Analyses

The safety subgroups in the Safety Analysis Set will be identified in the SAP.

11.4.4. Health Economics and Outcomes Research Data Analysis

The patient-reported outcomes (EORTC QLQ-C30, EQ-5D) and the health resource utilization data will be assessed based on a separate analysis plan. The plan will provide details of the descriptive and comparative statistical analyses.

11.4.5. Data Review by Data Monitoring Committee

A Data Monitoring Committee (DMC) (Section 15.9) will review all data relevant to safety (ie, AEs, SAEs, clinical laboratory values, exposure, genotyping, and concomitant medication information). Details will be provided in a separate DMC charter.

11.5. Sample Size Determination

The primary endpoint of the study is OS in the ITT Analysis Set. A log-rank test will be applied to test the treatment effect between the 2 treatment arms with a 2-sided alpha of 0.05.

For OS, a plateau effect was observed after 30 months of treatment in the control arm of the Midostaurin RATIFY study.[64] Therefore, a piecewise exponential model was considered to account for the plateau effect. Simulations were carried out to determine the sample size, timing of analysis, and power.

In the RATIFY study, the landmark survival rates of 42% at 30 months and 38% at 60 months in FLT3-ITD group were observed in the control arm.[65] This translates into a hazard rate of 0.029 in the first 30 months and 0.003 afterwards in the control arm. Based on this information, the simulation assumes a hazard rate of 0.029 in the first 30 months (from the randomization) and 0.003 afterwards in the placebo arm, and a HR of 0.7 and 1, respectively, before and after the first 30 months between the 2 treatment arms. This is equivalent to an assumed survival rate of 54% at 30 months and 50% at 60 months in the quizartinib arm.

Simulations indicate that about 84% power and 287 events will be obtained to achieve a statistically significant difference in OS distribution with approximately 536 subjects by a 2-sided log-rank test at the 0.05 significance level when OS is analyzed at 24 months after the last subject is randomized.

The OS analysis will be performed:

- When the target 287 OS events are observed and a minimum of 24 months has elapsed since the last subject was randomized.
- If the target 287 OS events are not achieved by 24 months since the last subject was randomized, then the analysis will be performed at a maximum of 30 months after the last subject is randomized.

The sample size derivation is based on the EAST Version 6.3 and simulations were run using SAS® Version 9.2.[66]

11.6. Statistical Analysis Process

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, quizartinib/placebo exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to un-blinding to preserve the integrity of the statistical analysis and clinical study conclusions.

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC 27513).[61]

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

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

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

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

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of Study Center facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

The investigator, sub-investigator, or study staff will enter the data in the eCRF.

The eCRF completion should be kept current and will be completed, and/or reviewed and e-signed by the investigator.

12.3. Data Management

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

To ensure the quality of clinical data across all subjects and Study Centers, a Clinical Data Management review will be performed on subject data according to specifications given to CRO. Data will be vetted both electronically and manually for eCRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated and resolved within the EDC application. During

this review, subject data will be checked for consistency, completeness, and any apparent discrepancies.

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

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA. All concomitant medications, prior cancer therapy will be coded using WHODD.

12.4. Study Documentation and Storage

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

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

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

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

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

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

12.5. Record Keeping

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

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).

- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the quizartinib/placebo (s) including acknowledgment of receipt at Study Center, accountability records and final reconciliation and applicable correspondence.

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

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

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

No study document should be destroyed without prior written agreement between Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) for the regions in which the study is being conducted.

15.2. Subject Confidentiality

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

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

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

15.3. Informed Consent

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

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

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

For studies in the US, an additional consent is required for the Health Insurance Portability and Accountability Act. Also, a separate special consent will be required for Pharmacogenomic testing for this protocol.

15.4. Regulatory Compliance

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

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The investigator and/or CRO must submit and, where necessary, obtain approval from the IEC or IRB for all subsequent protocol amendments and changes to the ICFs. The investigator should notify the IEC or IRB of deviations from the protocol or SAEs occurring at the Study Center and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authorities in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

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

15.5. Protocol Deviations

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

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

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

If a subject was ineligible or received the incorrect dose or quizartinib/placebo, and had at least 1 administration of quizartinib/placebo, data should be collected for safety purposes.

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

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

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, IECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

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

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

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study centers in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular Study Center(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The sponsor has the right to terminate the study at any time and the study termination may also be requested by (a) competent authority/ies.

Stopping criteria are noted in Section 5.9.2.

15.9. Data Monitoring Committee

An independent DMC will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring the progress and results. The DMC will comprise qualified physicians and scientists who are not investigators in the study and not otherwise directly associated with the Sponsor.

The DMC will periodically review unblinded safety and/or efficacy data in this study. The details about the reviews of the study data and other DMC processes will be described in the DMC charter.

The DMC may recommend modification of the study protocol or study to the Steering Committee based on pre-specified rules described in the DMC charter.

15.10. Independent Review Committee

An IRC will be established to independently review specified study endpoints (see Section 7.5). The composition, tasks and detailed operating process of the IRC will be described in detail in the IRC charter for this study.

15.11. Steering Committee

The Steering Committee will be comprised of academic representatives who are experts in the field of leukemia and senior representatives from the Sponsor. The Steering Committee has a scientific and clinical advisory function for the study and is not directly involved in operational matters. The responsibilities of the Steering Committee include:

- Review the protocol, amendments, and any substudies; and
- Provide guidance on key scientific, medical, strategic, and policy issues;

15.12. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in study reference materials.

16. REFERENCES

1. Larson RA, et al. An Analysis of Maintenance Therapy and Post-Midostaurin Outcomes in the International Prospective Randomized, Placebo-Controlled, Double-Blind Trial (CALGB 10603/RATIFY [Alliance]) for Newly Diagnosed Acute Myeloid Leukemia (AML) Patients with FLT3 Mutations. Oral Abstract #145: 59th ASH Annual Meeting and Exposition.
2. Quizartinib (AC220) Investigator's Brochure.
3. Cortes JE, Kantarjian H, Foran JM, et al. Phase 1 study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. J Clin Oncol. 2013; 31:3681-7.
4. Martinelli G, Perl AE, Dombret H, et al. Effect of quizartinib (AC220) on response rates and long-term survival in elderly patients with FLT3-ITD positive or negative relapsed/refractory acute myeloid leukemia. J Clin Oncol. 2013;31 (suppl): abstr 7021.
5. Cortes JE, Perl AE, Dombret H, et al. Response rate and bridging to hematopoietic stem cell transplantation (HSCT) with quizartinib (AC220) in patients with FLT3-ITD positive or negative relapsed/refractory AML after second-line chemotherapy or previous bone marrow transplant. J Clin Oncol. 2013;31 (suppl): abstr 7012.
6. Levis MJ, Cortes JE, Perl AE, et al. High Response Rate and Bridging to Hematopoietic Stem Cell Transplantation with Quizartinib (AC220) in Patients with FLT3-ITD-Positive Relapsed/Refractory Acute Myeloid Leukemia (AML). June 2013; The 18th Congress of the European Hematology Association; Poster P043.
7. Russell N, Tallman MS, Goldberg S, et al. Quizartinib (AC220) in Patients with FLT3-ITD(+) Relapsed or Refractory Acute Myeloid Leukemia: Final Results of a Randomized Phase 2 Study. June 2014; The 19th Congress of the European Hematology Association; Abstract 333 tract 187. http://www.ambitbio.com/Posters/EHA%20Poster%20Russell%209%20June%202014_FINAL.pdf
8. Schiller G, Tallman MS, Goldberg S, et al. Final Results of a Randomized Phase 2 Study Showing the Clinical Benefit of Quizartinib (AC220) in Patients with FLT3-ITD Positive Relapsed or Refractory Acute Myeloid Leukemia. June 2014; American Society of Clinical Oncology Annual Meeting; Abstract 385. http://www.ambitbio.com/Posters/ASCO%20Poster%20Dr%20Schiller%2029%20May%202014_FINAL.pdf
9. Altman JK; Foran JM, Pratz KW, et al. Results of a Phase 1 Study of Quizartinib (AC220, ASP2689) in combination with induction and consolidation chemotherapy in younger patients with newly diagnosed acute myeloid leukemia. 2013; ASH Annual Meeting and Exposition; Abstract 623.
10. Burnett et al., Presentation: AC220 (Quizartinib) Can Be Safely Combined with Conventional Chemotherapy in Older Patients With Newly Diagnosed Acute Myeloid Leukaemia: Experience From The AML18 Pilot. Blood. 2013;122(21):Abstract 622.

11. Brunet S, Martino R, Sierra J. Hematopoietic transplantation for acute myeloid leukemia with internal tandem duplication of FLT3 gene (FLT3/ITD). Curr Opin Oncol. 2013;25:195-204.

12. Stone R. Acute myeloid leukemia in first remission: to choose transplantation or not? J Clin Oncol. 2013;31(10):1262-6.

13. Sandmaier BM, Khaled SK, Oran B, et al. Results of a Phase 1 Study of Quizartinib (AC220) As Maintenance Therapy in Subjects with Acute Myeloid Leukemia in Remission Following Allogeneic Hematopoietic Cell Transplantation. 2014; ASH Annual Meeting and Exposition; Abstract 428. https://ash.confex.com/ash/2014/webprogram/Paper73502.html

14. Carow CE, Levenstein M, Kaufmann SH, et al. Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. Blood. 1996;87:1089-96.

15. Drexler HG. Expression of FLT3 Receptor and Response to FLT3 Ligand by Leukemic Cells. Leukemia. 1996;10(4):588-99.

16. Gilliland G, Griffin JD. The Roles of FLT3 in Hematopoiesis and Leukemia. Blood 2002; 100:1532-42.

17. Levis M, Small D. FLT3 Tyrosine Kinase Inhibitors. Intl J Hematol. 2005;82(2):100-7.

18. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood. 2001; 98(5):1312-20.

19. Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood. 2011;117(12):3294-301.

20. Fischer T, Stone RM, DeAngelo DJ, et al. Phase IIB Trial of Oral Midostaurin (PKC412), the FMS-Like Tyrosine Kinase 3 Receptor (FLT3) and Multi-Targeted Kinase Inhibitor, in Patients with Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome With Either Wild-type or Mutated FLT3. J Clin Oncol. 2010;28(28):4339-45.

21. Cairoli R, Grillo G, Beghini A, et al. c-KIT Point Mutations in Core Binding Factor Leukemias: Correlation with White Blood Cell Count and the White Blood Cell Index. Leukemia. 2003;17:471-2.

22. Kindler T, Breitenbuecher F, Marx A, et al. Efficacy and Safety of Imatinib in Adult Patients with c-KIT-Positive Acute Myeloid Leukemia. Blood. 2004;103(10):3644-54.

23. Cammenga J. Horn S, Bergholz U, et al. Extracellular KIT Receptor Mutants, Commonly Found in Core Binding Factor AML, are Constitutively Active and Respond to Imatinib Mesylate. Blood. 2005;106:(39)58-61.

24. NCCN Guidelines (Version 1.2015). http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

25. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m^2 versus 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood. 2015;125(25):3878-85.

26. Burnett AK, Russell NH, Hills RH, et al. Optimization of Chemotherapy for Younger Patients with Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial. J Clin Oncol. 2013; 31 (27) 3360.

27. Othake S, Miyawaki S, Fujita H, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. Blood 2011;117(8):2358-65.

28. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med. 2009 Sep 24;361(13):1249-59.

29. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361(13):1235-48.

30. Döehner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-74.

31. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive Postremission Chemotherapy in Adults with Acute Myeloid Leukemia. N Engl J Med. 1994;331:896-903.

32. Nepomuceno R, Rooks A, Gardner M, et al. Differential inhibition of FLT3-ITD, FLT3-WT and KIT by quizartinib as assessed by modified PIA Assay. Blood. 2014;124(21):951.

33. Sato T, Yang X, Knapperet S, et al. FLT3 ligand impedes the efficacy of FLT3 inhibitors in vitro and in vivo. Blood. 2011;117(12): 3286-93.

34. Yang X, Sexauer A, and Levis M. Bone marrow stroma-mediated resistance to FLT3 inhibitors in FLT3-ITD AML is mediated by persistent activation of extracellular regulated kinase. Br. J. Haematol. 2014;164 (1):61-72.

35. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 Guidance http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf

36. WHO International Classification of Disease for Oncology. Third edition. First revision. 2008 from: http://apps.who.int/iris/bitstream/10665/96612/1/9789241548496_eng.pdf?ua=1

37. Cohen PR. Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007 Jul 26;2:34.

38. Fathi AT, Le L, Hasserjian RP, et al. FLT3 inhibitor-induced neutrophilic dermatosis. Blood. 2013 Jul 11;122(2):239-42. doi: 10.1182/blood-2013-01-478172. Epub 2013 May 17.

39. Varadarajan N, Boni A, Elder DE, et al. FLT3 Inhibitor-Associated Neutrophilic Dermatoses. JAMA Dermatol. 2016 Apr;152(4):480-2. doi: 10.1001/jamadermatol.2015.6121.

40. Callen JP. Pyoderma gangrenosum. Lancet. 1998 Feb 21;351(9102):581-5.

41. Jha PK, Rana A, Kapoor S, et al. Pyoderma gangrenosum in a renal transplant recipient: A case report and review of literature. Indian J of Neph. 2015;25(5):297-299. doi:10.4103/0971-4065.156900.

42. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 Trial. Blood. 2001;98:1312-20.

43. Center for International Blood & Marrow Transplant Research. Q19-44: Graft versus Host Disease (Allogeneic Only). In: CIBTR.org. Forms Instruction Manual: 2020. p. 326-43.

44. Jagasia MH, Greinix HT, Arora M. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21(3): 389–401.e1.

45. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised Recommendations of the International Working Group for diagnosis, Standardization of response Criteria, Treatment Outcomes, and reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.

46. Luskin MR, Lee J, Fernandez HF, et al. Results of the ECOG E1900 Trial in Younger Adults with AML Using an Event Free Survival Endpoint Are Concordant with Results Based on Overall Survival: Potential for a Surrogate Endpoint to Facilitate Rapid Approval of Therapies in AML. 2014; ASH Annual Meeting and Exposition; Abstract 2599. https://ash.confex.com/ash/2014/webprogram/Paper69426.html

47. Keating MJ, Kantarjian H, Smith TL, et al. Response to salvage therapy and survival after relapse in acute myelogenous leukemia. J Clin Oncol. 1989;7(8):1071-80.

48. FDA. Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

49. Redaelli A, Stephens JM, Brandt S, et al. Short- and long-term effects of acute myeloid leukemia on patient health-related quality of life. Cancer Treatment Reviews 2004;30:103-17.

50. Schumacher A, Kessler T, Büchner T, et al. Quality of life in adult patients with acute myeloid leukemia receiving intense and prolonged chemotherapy – a longitudinal study. Leukemia. 1998;12:586-92.

51. Zimmermann C, Yuen D, Mischitelle A, et al. Symptom burden and supportive care in patients with acute leukemia. Leukemia Research. 2013;37:731-6.

52. Appelbaum FR, Rosenblum D, Arceci RJ, et al. End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood. 2007;109:1810-6.

53. Fayers P and Bottomley A, on behalf of the EORTC Quality of Life Group and of the Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. EU Jrn Can. 2002;38:125-133.

54. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 [28 May 2009]. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_403

55. Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. (July, 2009). Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

56. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guidelines. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Current Step 4 Revision. 27 October 1994. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

57. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. QOL Res. 1996;5(6):555-67.

58. Alibhai SMH, Leach M, Kermalli H, et al. The impact of acute myeloid leukemia and its treatment on quality of life and functional status in older adults. Crit Rev in Onc/Hema. 2007;64(1):19-30.

59. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20(10):1727-36.

60. Brookmeyer R and Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982;38(1):29-41.

61. SAS PROC LIFETEST. SAS/STAT(R) 9.2 User's Guide, Second Edition. Available from: http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_lifetest_sect004.htm

62. Newcombe, RG. Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. Statist Med. 1998;17:857-72.

63. European Medicines Agency. Guideline on the clinical evaluation of anticancer medicinal products. EMA/CHMP/205/95 Rev.6. Draft Guidance. 05 Jan 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf

64. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017;377:454-64.

65. Stone RM, Mandrekar S, Sanford BL, et al. The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance]). Blood. 2015;126(23):6.

66. Cytel. Cytel Launches East® Version 6.3 for Adaptive Dose-Escalation Studies and Accurate Interim Trial Prediction. Available at: http://www.cytel.com/hubfs/0-library-0/pdfs/East6.3-Release-Announcement-FINAL-071514.pdf

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

68. Credible Meds. Combined List of Drugs That Prolong QT and/or Cause Torsades de Pointes (TdP). Last Revised: September 15, 2015 https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf

69. Flockhart DA (2007). Drug Interactions: Cytochrome P450 Drug Interaction Table. http://medicine.iupui.edu/clinpharm/ddis/main-table. Indiana University School of Medicine.

70. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

71. Döhner H, Estey E, Grimwade D, et al. Diagnosis and Management of AML in Adults: 2017 ELN Recommendations from an International Expert Panel. Blood. 2016. Epub 2016 Nov 28.

72. FDA. Guidance for Industry. Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment. Draft Guidance. August 2020. https://www.fda.gov/media/140821/download

73. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

74. Calcium correction for hypoalbuminemia Available from: https://www.omnicalculator.com/health/corrected-calcium#corrected-calcium-equation-calculator.